Invited Review

CROI 2022: Advances in Antiviral Therapy for HIV, COVID-19, and Viral Hepatitis

Shauna H. Gunaratne, MD, MPH[1]; Hong-Van Tieu, MD, MS[1,2]; Timothy J. Wilkin, MD, MPH[3]; Barbara S. Taylor, MD, MS[4]

[1]Columbia University Irving Medical Center, New York, New York
[2]New York Blood Center, New York, New York
[3]Weill Cornell Medicine, New York, New York
[4]University of Texas Health Science Center at San Antonio

The 2022 Conference on Retroviruses and Opportunistic Infections provided a rich source of new data and comprehensive reviews on antiviral therapy. For COVID-19, intramuscular sotrovimab was noninferior to intravenous sotrovimab, serostatus did not predict the efficacy of sotrovimab, and molnupiravir appeared safe and modestly effective in decreasing hospitalization rates. Trials from low- and middle-income countries provided data to support transitioning those on first-line therapy with or without virologic suppression and those virologically suppressed on second-line therapy to dolutegravir-based regimens. Additional data supported the use of lenacapavir as a long-acting antiretroviral drug. Data across the United States demonstrate the negative impact of the COVID-19 pandemic on the HIV care continuum, although enhanced outreach efforts and decentralization of antiretroviral therapy delivery were associated with improvements in care engagement outcomes. Researchers described potential mechanisms for the emergence of integrase strand transfer inhibitor resistance. Studies on proviral genotyping highlighted the limitations of its use in predicting clinically significant resistance. Several studies looked at the epidemiology and treatment of hepatitis C and B and the status of current hepatitis C virus elimination efforts. Data presented on HIV, COVID-19, and maternal and pediatric health included 2-year virologic outcome data of very early antiretroviral therapy in potentially reducing the latent HIV reservoir in infants with HIV. Data presented on COVID-19 and HIV therapeutics in children included SARS-CoV-2–neutralizing monoclonal antibodies in children younger than 12 years of age, remdesivir in hospitalized infants and children, and long-acting therapies for HIV treatment in children.

Author Correspondence
Send correspondence to Dr Shauna Gunaratne, 180 Fort Washington Ave, 6th Floor, New York, NY, 10032, or email shg2130@cumc.columbia.edu.

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Advances in Treatment of COVID-19

Antivirals and Monoclonal Antibodies for Treatment of Nonhospitalized Patients With COVID-19

Kumarasamy and colleagues presented results from a phase III trial of molnupiravir for treatment of mild SARS-CoV-2 in India (Abstract 101). Their multicenter, open-label, randomized controlled trial enrolled more than 1200 adults with mild SARS-CoV-2 infection within 5 days of symptom onset and confirmed SARS-CoV-2 positive results by reverse transcriptase polymerase chain reaction (RT-PCR). Patients were randomly assigned to receive oral molnupiravir 800 mg twice daily or standard of care.

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The primary endpoint of hospitalization by day 14 was reached in 1.5% of patients (9 patients) in the treatment arm compared with 4.3% (26 patients) in the standard of care arm, which was statistically significant (P=.0053). They also observed a faster time to clinical improvement, increased rates of SARS-CoV-2 negativity, and reduced viral loads (inferred from cycle thresholds) in the treatment arm compared with the standard of care arm. They did not observe an increased rate of serious adverse events in the investigational arm. These results were similar to observations from a randomized controlled trial conducted in the United States, where modest improvements in rates of hospitalization or death were seen.[1]

Strizki presented data on errors in SARS-CoV-2 RNA with the use of molnupiravir from the MOVe-OUT (Efficacy and Safety of Molnupiravir in Non-Hospitalized Adult Participants With COVID-19) trial (Abstract 471). Molnupiravir's mechanism of action is to insert mutations into the viral RNA, thereby inhibiting viral replication. The authors observed a statistically significant increase in the mean number of mutations in the molnupiravir 800 mg group compared with the placebo group (P<.0001). The majority of mutations observed were transition errors. After molnupiravir treatment, the authors observed a few mutations but no change in susceptibility to molnupiravir. They observed 11 spike protein mutations in 6 of the study participants who received molnupiravir, and reported that all mutations were seen in previously circulating virus. The authors concluded that no mutations associated with molnupiravir resistance or any treatment-emergent mutations in the spike protein were found that had not been previously observed without the presence of molnupiravir.

The study authors did not find any mutations associated with molnupiravir resistance or any treatment-emergent mutations in the spike protein that had not previously been observed without the presence of molnupiravir

Kohli presented results from the COMET-TAIL (COVID-19 Monoclonal Antibody Efficacy Trial – Treatment of Acute COVID-19 with Intramuscular Monoclonal Antibody) trial, a phase III randomized, controlled, noninferiority study examining intramuscular (IM) versus intravenous (IV) sotrovimab (Abstract 102). The investigators enrolled patients who were at least 12 years of age with COVID-19 with symptoms within 7 days of onset and who were at high risk of progression, including those who were at least 55 years of age or had comorbidities such as diabetes, chronic kidney disease, chronic lung disease, chronic liver disease, and immunosuppression. The investigators initially had 3 arms comparing IV sotrovimab 500 mg, IM sotrovimab 500 mg, and IM sotrovimab 250 mg, but the IM sotrovimab 250 mg arm was discontinued due to an increased rate of hospitalization compared with the other 2 arms. The primary endpoint was all-cause hospitalization by day 29. Of note, enrollment had been completed by August 2021, so they primarily studied the effect of sotrovimab on the Delta variant before the rise of the Omicron variant. The adjusted risk difference was 1.07% (95% confidence interval [CI], –1.25%-3.39%) between IM sotrovimab 500 mg and IV sotrovimab 500 mg. The IM formulation was noninferior to the IV formulation based on the prespecified margin of 3.5%. The investigators observed a low rate of adverse events and injection site reactions in the IM group.

Shapiro presented results from the COMET-ICE (COVID-19 Monoclonal Antibody Efficacy Trial – Intent to Care Early) trial, which examined the effect of positive baseline SARS-CoV-2 anti-nucleocapsid (N) antibody on response to sotrovimab (Abstract 103). N immunoglobulin G (IgG) antibody was obtained on the first day of the study, before any infusion was administered. The patient population studied was unvaccinated adults at least 55 years of age or unvaccinated adults at least 18 years of age with a comorbid condition, and with COVID-19

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within 5 days of symptom onset. Patients with a history of prior COVID-19 were not enrolled. Of note, patients were enrolled through March 2021, before the emergence of the Delta or Omicron variants. The primary outcome was all-cause hospitalization rates by day 29. The investigators observed decreases in hospitalization rates in seropositive and seronegative groups that were consistent with the overall study population. They noted lower baseline SARS-CoV-2 viral loads and a trend toward lower rates of hospitalization in seropositive patients, but firm conclusions were limited due to the small number of patients observed. The study authors noted that sotrovimab appeared to reduce progression to severe COVID-19 and hospitalization despite serostatus. Serostatus testing did not appear to be useful in the outpatient setting in predicting which patients may respond better to sotrovimab, unlike in the RECOVERY (Randomised Evaluation of COVID-19 Therapy) trial, which showed that negative serostatus was correlated with decreased mortality when casirivimab (CAS) and imdevimab (IMD) were evaluated in hospitalized patients.[2]

O'Brien and colleagues presented results from a phase III randomized, double-blind, placebo-controlled trial examining the use of CAS/IMD as pre-exposure prophylaxis in household contacts of patients with COVID-19, with infusions administered within 96 hours of the index case's positive RT-PCR result (Abstract 104). The primary outcome was the proportion of patients who developed SARS-CoV-2 infection confirmed by RT-PCR (irrespective of presence of symptoms). Of note, this study completed enrollment in October before the emergence of the Omicron variant, and it enrolled primarily during the era of the Delta variant. The investigators observed an 81.2% risk reduction of symptomatic SARS-CoV-2 infections with the use of CAS/IMD (odds ratio [OR], 0.17; 95% CI, 0.09-0.31; $P<.0001$) and a 68.2% risk reduction of symptomatic or asymptomatic SARS-CoV-2 infection (OR, 0.27; 95% CI, 0.20-0.37; $P<.0001$). The investigators observed a protective effect up to 5 months after administration, with waning efficacy 6 to 8 months after administration. When limiting the observation period to 5 months (when the CAS/IMD was found to be fully protective), there was a 100% risk reduction of symptomatic SARS-CoV-2 infections and an 89.5% risk reduction of all SARS-CoV-2 infections.

Jilg and colleagues conducted a phase II trial looking at efficacy outcomes for camostat, a serine protease inhibitor that inhibits SARS-CoV-2 in vitro (Abstract 105). When looking at outcomes of hospitalization or death, they did not see any significant difference in the event rate between the camostat arm (5.6%) and the placebo arm (4.7%) ($P=.76$). They also did not observe any significant difference in time to virologic clearance and time to symptom improvement. The authors concluded that camostat did not show any efficacy for treatment of SARS-CoV-2. Jilg and colleagues presented data from a second placebo-controlled trial of camostat for the treatment of outpatients with COVID-19 and a high risk of progression (Abstract 459). They randomly assigned 295 participants (57% female, 60% Hispanic, 7% Black). Progression to hospitalization or death was low in the camostat and placebo groups (5.3% and 6.1%, respectively). There were nondefinitive trends toward faster clearance of SARS-CoV-2 infection by PCR. Based on these results, it appears that camostat should not be pursued further for treatment of COVID-19.

The study authors concluded that camostat did not show any efficacy for treatment of SARS-CoV-2

Taiwo and colleagues presented data on SAB-185, a bovine-derived, fully human polyclonal immunoglobulin, studied in nonhospitalized patients with mild to moderate symptomatic COVID-19 infection (Abstract 454). Two hundred thirteen participants were randomly assigned to the SAB-185 arm or the placebo arm (median age, 38 years; 54% women; 50% Hispanic; 7% Black). The investigators found no difference in the proportion of participants with SARS-CoV-2 RNA suppression over 2 weeks, and no difference in time to resolution of symptoms.

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Webb and colleagues reported on the safety of remdesivir in a placebo-controlled trial of 562 nonhospitalized patients with COVID-19 at high risk of progression (Abstract 456). The primary efficacy results showing an 87% reduction in COVID-19–related hospitalization or death with remdesivir have been published.[3] Remdesivir was dosed as 200 mg intravenously on day 1, and 100 mg on days 2 and 3. Remdesivir recipients experienced a slightly higher rate of drug-related nausea (6.5% vs 3.5%), and a grade 3 or greater decrease in creatinine clearance (5.6% vs 1.9%). The creatinine levels generally remained in the normal range, and the changes in clearance resolved in follow-up. Other adverse events were generally similar between groups. The authors concluded that remdesivir was safe and well tolerated in outpatients at high risk for progression.

Remdesivir appears safe and well tolerated in nonhospitalized patients with COVID-19

Nomah and colleagues investigated the potential benefit of tenofovir disoproxil fumarate (TDF)/emtricitabine (FTC) for modifying COVID-19 infection and disease among people with HIV (Abstract 469). They performed a propensity score-matched analysis within an ongoing cohort study. They compared patients receiving TDF/FTC, tenofovir alafenamide (TAF)/FTC, and abacavir/lamivudine (ABC/3TC). There was a suggestion that patients receiving TDF/FTC may be less likely to have a SARS-CoV-2 diagnosis, but patients receiving TAF/FTC had similar rates of SARS-CoV-2 to patients receiving ABC/3TC. The authors concluded that the differences observed with TDF/FTC were likely due to more favorable baseline prognostic factors, and that these data did not support a role for tenofovir to modify SARS-CoV-2 infection or disease.

Data did not support a role for tenofovir in preventing or modifying SARS-CoV-2 infection

Treatment of Hospitalized Patients With COVID-19

Investigators from the PAN-COVID (Global Pregnancy and Neonatal Outcomes in COVID-19) study group presented a randomized, factorial study comparing TDF/FTC with no TDF/FTC, and baricitinib plus dexamethasone versus dexamethasone alone (Abstracts 460 and 463). They randomly assigned 355 adults with COVID-19 (97% hospitalized; 72% with 1 or more comorbidity; 65% male; median age, 67 years). There was no significant difference between TDF/FTC versus no TDF/FTC with regard to mortality (2.2% vs 4%, respectively) or disease progression (22.5% vs 20.3%, respectively). The authors concluded that TDF/FTC did not improve outcomes. Of the 355 participants, 287 (81%) were randomly assigned to baricitinib plus dexamethasone or dexamethasone alone. Baricitinib is a Janus kinase 1 inhibitor that inhibits intracellular signaling pathways of several cytokines known to be increased in COVID-19. Baricitinib accelerated recovery time for COVID-19, especially for those participants on noninvasive ventilation, in a clinical trial enrolling 1033 participants.[4] In this trial, several clinical para meters favored baricitinib, but none reached statistical significance.

Two analyses investigated the role of monoclonal antibodies targeting the interleukin (IL)-6 receptor in patients with severe COVID-19. Mussini and colleagues reported on a cohort of 992 patients who did or did not receive tocilizumab for progressive disease (Abstract 465). There was no difference in mortality in the unadjusted analysis. Several analyses adjusted for various disease severity markers and demographic data suggested a survival benefit with tocilizumab. Any potential benefit from tocilizumab was limited to those with a C-reactive protein (CRP) level greater than 7.5 mg/dL, and there was a suggestion of harm in patients with lower CRP concentrations. Mastrorosa and colleagues presented data on a randomized, open-label trial of sarilumab for treatment of severe COVID-19 (Abstract 466). One

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hundred seventy-six participants were randomly assigned 2:1 to sarilumab plus standard of care or standard of care alone. The primary endpoint was time to a 2-point improvement on the 7-point COVID-19 ordinal scale. The investigators did not find an overall benefit to sarilumab. There was a suggestion of potential benefit in the group with CRP concentrations less than 7 mg/dL. The reason for these somewhat disparate findings is not clear.

Treatment Outcomes for COVID-19

Price and colleagues from the National COVID Cohort Collaborative (N3C) pooled data from 3,766,433 people with COVID-19 from 69 centers across the United States to determine which therapy or combination of therapies for COVID-19 are associated with hospital discharge at week 4 (Abstract 637). The analysis used elastic net penalized multinomial logistic regression to determine probabilities of treatment effects for different ordinal scale outcomes for COVID-19, but did not find any standard combination of treatments that predicted discharge by week 4. Steroids with or without monoclonal antibodies, antibiotics, or antivirals, depending on the Charlson comorbidity index and timeframe, were most effective for those hospitalized on ventilators, extracorporeal membrane oxygenation, or vasopressors. Combinations without steroids but including antivirals, monoclonal antibodies, or anticoagulants appeared most effective for those hospitalized with or without oxygen supplementation. The investigators did note an impact of the Delta variant compared with previous variants on the effectiveness of various regimens. For example, anticoagulants only appeared in some of the most effective treatment combinations in the post-Delta variant era. These data suggest there are many possible effective therapeutic options for COVID-19 treatment, and disease severity and variants will continue to influence response to treatments.

Data from the N3C were used to explore the effect of HIV diagnosis on COVID-19 hospitalizations and mortality, and the impact of age on these outcomes (Abstract 901). Of 2,422,864 adults with COVID-19 in the cohort, 15,188 (0.62%) were people with HIV. Investigators created an exact matched cohort matching people with HIV to those without HIV on age, sex, race, and ethnicity and found people with HIV had higher odds of hospitalization (OR, 1.50; 95% CI, 1.42-1.58) and death (OR, 1.48; 95% CI, 1.29-1.69) than those without HIV. A propensity score matching analysis demonstrated that people with HIV had a higher risk of hospitalization until the age difference reached 13 years, and a higher risk of death until the age difference reached 6 years. When people with HIV were stratified by CD4+ cell count, age thresholds for those with CD4+ counts under 200 cells/μL were reduced to 6 years for hospitalization but extended to 11 years for death. These findings suggest that the acceleration of aging known to be present for people with HIV may lead to the elevated risk of hospitalization and death from COVID-19, and that immunodeficiency, based on CD4+ cell count, likely also impacts those outcomes.

Lenacapavir as a part of combination regimen led to sustained virologic suppression in patients living with HIV

Advances in Treatment of HIV

Investigational Agents

Lenacapavir. Gupta and colleagues presented data from the CALIBRATE (Study to Evaluate the Safety and Efficacy of Lenacapavir in Combination With Other Antiretroviral Agents in People Living With HIV) trial on various lenacapavir (LEN)-based regimens in treatment-naive people with HIV (Abstract 138). The study enrolled 182 people with CD4+ count above 200 cells/μL and plasma HIV RNA level above 200 copies/mL who had never received antiretroviral therapy (ART) (median age, 29 years; 7% female; 52% Black; 45% Hispanic). Participants were enrolled into 1 of 4 groups. Groups 1 and 2 received LEN orally for 2 weeks followed by

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subcutaneous injections given every 6 months with daily TAF/FTC through week 28. At week 28, group 1 continued daily TAF without FTC and subcutaneous LEN. Group 2 continued subcutaneous LEN and changed TAF/FTC to bictegravir (BIC) daily. Group 3 received LEN orally and daily TAF/FTC through week 54, and group 4 received BIC/FTC/TAF through week 54. The week 28 results were previously presented, wherein 94% in the LEN groups achieved a plasma HIV RNA level below 50 copies/mL. For those suppressed at week 28, all groups exhibited high rates of viral suppression at week 54, ranging from 90% to 94%. Resistance to LEN emerged in 2 participants: 1 at week 10 and a second at week 54. Both participants had evidence of nonadherence to TAF/FTC. Three participants discontinued LEN due to injection site reactions. These preliminary data support the continued evaluation of LEN for treatment of HIV, including its use in novel 2-drug regimens.

Ogbuagu and colleagues presented additional data on LEN for the treatment of multidrug-resistant (MDR) HIV from the CAPELLA (Study to Evaluate the Safety and Efficacy of Lenacapavir in Combination With an Optimized Background Regimen [OBR] in Heavily Treatment Experienced Participants Living With HIV-1 Infection With Multidrug Resistance) trial (Abstract 491). This study enrolled participants with ongoing viremia who had resistance to 2 or more drugs in 3 or more major drug classes. The results combined a cohort randomly assigned to LEN or placebo for 14 days and a nonrandomized cohort. The authors presented week 52 data; the week 26 data had been previously presented. The analysis included 72 participants (25% female; 38% Black; 21% Hispanic; median age, 52 years). The median plasma HIV RNA level was 4.5 $\log_{10}$ copies/mL, and 64% had a CD4+ count less than 200 cells/μL. Overall, 81% had a plasma HIV RNA level below 50 copies/mL at week 52 (88% below 200 copies/mL). LEN appeared well tolerated, with only 1 person withdrawing due to injection site reactions. These data support the use of LEN for patients with MDR HIV infection.

Broadly neutralizing antibodies. Juelg and colleagues presented the antiviral activity of 3 broadly neutralizing antibodies (bNAbs): PGDM1400, PGT-121, and VRC07-523LS (Abstract 139). Four participants received the triple combination. The investigators observed a mean decline of 1.76 $\log_{10}$ copies/mL through 7 days. One participant was lost to follow-up while having a declining plasma viral load through 25 days. The other participants exhibited viral rebound between 13 and 70 days postinfusion. Two of the 3 participants had reduced susceptibility to 1 or more antibodies at baseline. All participants showed reduced susceptibility at failure of 1 or more bNAbs compared with baseline.

Caskey and colleagues presented data on the antiviral activity of a combination of 2 bNAbs, 10-1074LS and 3BNC117-LS, in people with HIV (Abstract 140). Participants were required to be off ART or never treated. They enrolled 6 participants with a median CD4+ count of 523 cells/μL and a median plasma HIV RNA level of 48,700 copies/mL. All participants received single infusions of the 2 bNAbs. Four participants showed a transient decline in plasma HIV RNA of approximately 1.9 $\log_{10}$ copies/mL. The other 2 participants showed sustained viral suppression for 16 and 24 weeks, respectively. Phenotypic testing of HIV DNA revealed that the 4 participants with transient declines in viremia had predicted resistance to 1 or both antibodies, although the 2 achieving suppression had predicted sensitivity to both antibodies. Of note, these participants also had lower viral loads at baseline.

Casazza and colleagues presented data on an adenoviral vector transferring a gene encoding VRC07, a bNAb targeting HIV (Abstract 498). They enrolled 8 participants with HIV on suppressive ART who received 1 of 3 doses of the adenoviral vector. The vector appeared safe in this small study. It led to detectable VRC07 concentrations, which were sustained through 3 years of follow-up. Higher concentrations were observed at the higher doses. A few participants developed antidrug antibodies to VRC07 that reduced concentrations. The antibodies generated from the gene transfer exhibited expected functionality in ex vivo experiments. Although therapeutic concentrations of VRC07 were not achieved in this study, it does provide

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proof-of-concept of a gene transfer approach to induce production of bNAbs.

Long-acting cabotegravir and rilpivirine. Overton and colleagues presented additional data from the ATLAS-2M (Long-acting Cabotegravir and Rilpivirine Dosed Every 2 Months in Adults With HIV-1 Infection) trial that compared outcomes with every-4-week and every-8-week dosing of long-acting cabotegravir and rilpivirine (CAB-LA/RPV) (Abstract 479). Participants in this trial were enrolled from the oral ART arm and CAB-LA/RPV arm of the ATLAS trial, as well as de novo participants who were suppressed on oral ART. Overall, 85.9% and 87.4% at week 152 in the every-4-week and every-8-week arm, respectively, had plasma HIV RNA level below 50 copies/mL. The reasons for nonsuppression in the 2 groups appeared somewhat different, with more participants leaving the study with a plasma HIV RNA viral load of more than 50 copies/mL in the every-8-week group. However, participants in the every-4-week group were more likely to choose to leave the study; the treatment satisfaction was substantially greater among participants in the every-8-week group. A total of 13 participants had resistance emerge through week 152; 11 were in the every-8-week group, and 2 were in the every-4-week group. These data support the long-term efficacy of and participant satisfaction with the every-8-week regimen.

Clinical trials of second-line therapy in low- and middle-income countries. Mulenga and colleagues presented results from the VISEND (Dolutegravir With Recycled nRTIs Is Noninferior to PI-based ART) study, which enrolled Zambian people with HIV currently receiving TDF, 3TC, and efavirenz (EFV) or nevirapine (NVP) (Abstract 135). Overall, 1201 participants were enrolled (61% female; median age, 40 years). Participants were divided into group A or group B based on plasma HIV RNA (<1000 copies/mL and ≥1000 copies/mL, respectively). In group A, 418 participants were randomly assigned to TDF/3TC/dolutegravir (DTG) or TAF/FTC/DTG. At week 48, 80% and 74%, respectively, were below 50 copies/mL using the intention-to-treat (ITT) analysis. TAF/FTC/DTG did not achieve noninferiority to TDF/3TC/DTG in this study using an HIV RNA cutoff of less than 50 copies/mL but did achieve noninferiority using a 1000 copies/mL cutoff. Group B randomly assigned 773 participants to TDF/3TC/DTG, TAF/FTC/DTG, or the standard of care regimen (zidovudine, lamivudine, and atazanavir/ritonavir or lopinavir/ritonavir). At week 48, 72%, 80%, 70%, and 56% of participants had plasma HIV RNA less than 50 copies/mL in the TDF/3TC/DTG, TAF/FTC/DTG, atazanavir, and lopinavir arms, respectively. TAF/FTC/DTG appeared superior to TDF/3TC/DTG in this study using the less than 50 copies/mL cutoff. TAF/FTC/DTG and TDF/3TC/DTG each appeared superior to the combined protease inhibitor (PI) arms. The authors concluded that the data support the use of DTG with TAF/FTC or TDF/3TC for patients switching off a first-line nonnucleoside reverse transcriptase inhibitor (NNRTI)-based regimen.

Engamba and colleagues reported the outcomes of enhanced adherence counseling (3 adherence counseling sessions over 3 months) for participants who experienced virologic failure in the VISEND trial (Abstract 490). They found that 66% of participants achieved subsequent viral suppression (78% and 71% for the TAF/FTC/DTG and TDF/3TC/DTG arms, respectively; 62% and 53% for the atazanavir and lopinavir arms, respectively).

Paton and colleagues presented follow-up data from the NADIA (Nucleosides and Darunavir/Dolutegravir in Africa) trial (Abstract 137). This trial randomly assigned patients in whom a NNRTI, TDF, and 3TC or FTC was failing in a factorial design to receive TDF/3TC or zidovudine/3TC, and to receive DTG or darunavir/ritonavir. The week 48 results have been published.[5] The trial enrolled 464 participants (61% female). At week 96, 89.8% of the DTG group and 86.9% of the darunavir group had plasma HIV RNA viral loads of fewer than 400 copies/mL. This result was consistent in a variety of subgroup analyses. In particular, the viral suppression rates were similar among those with 0 or 1 active NNRTIs in their assigned regimen. DTG-based regimens led to sustained virologic suppression as second-line therapy even with significant NNRTI resistance. The viral suppression rates appeared lower among those with 2 active NNRTIs, likely because this group is

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enriched for those with nonadherence. Those receiving TDF had superior virologic outcomes to those receiving zidovudine. In the subgroup analyses, TDF maintained similar rates of efficacy when having varying amounts of NNRTI resistance at baseline including the K65R mutation. No resistance to darunavir was detected in study follow-up. Nine participants developed DTG resistance: 6 received zidovudine (5 with high-level DTG resistance), and 3 received TDF (none with high-level resistance). The authors concluded that DTG and TDF/3TC give durable suppression as second-line therapy even if there are no predicted active NNRTIs. They also noted that DTG resistance was a concern that may be reduced by using TDF/3TC instead of zidovudine/3TC.

DTG-based regimens led to sustained virologic suppression as second-line therapy even with significant NNRTI resistance

Ombaja and colleagues reported on a randomized controlled trial enrolling virally suppressed individuals suppressed on a second-line PI-based regimen (Abstract 136). Participants (n=791) were randomly assigned to switch to TDF/3TC/DTG or to maintain their current PI-based regimen. Of note, there were no available resistance data for participants. Participants included 66% women with a median age of 46 years. The primary endpoint was proportion with plasma HIV RNA greater than 50 copies/mL according to the US Food and Drug Administration (FDA) snapshot regimen. This occurred in 5.0% and 5.1% of the TDF/3TC/DTG and PI arms, respectively, meeting the protocol definition of noninferiority. There were no obvious differences in adverse events between the 2 groups. The authors concluded that switching virally suppressed patients on second-line therapy to TDF/3TC/DTG was safe and efficacious even in the absence of prior resistance data. This provides further support to current World Health Organization (WHO) recommendations.

Additional cohort data on first-line therapy in low- and middle-income countries. McCluskey and colleagues presented on outcomes on Ugandan patients with HIV on first-line regimens who transitioned to TDF/3TC/DTG (Abstract 487). Among 500 people, 95% had plasma HIV RNA suppressed with less than 50 copies/mL at the time of transition. At 1 year, 92% were virally suppressed and in care, 5% had plasma HIV RNA of 50 copies/mL or greater (median, 252 copies/mL), 2% were lost to follow-up, and 1% died. In addition, 3% of participants discontinued TDF/3TC/DTG prior to week 48.

Kityo and colleagues presented data from ACTG (AIDS Clinical Trial Group) A5381, the HAKIM (Observational Cohort to Assess Therapeutic Efficacy and Emergence of HIV Drug Resistance Following Initiation of Tenofovir-Lamivudine-Dolutegravir for First- or Second-Line ART or With Rifampin-Containing TB Treatment) study (Abstract 488). This study will describe the efficacy and development of resistance occurring in the setting of TDF/3TC/DTG rollout globally. In this analysis, they reported on the 6-month outcomes of people with HIV initiating TDF/3TC/DTG as a first regimen (n=179), and patients with virologic suppression on a first-line regimen switching to TDF/3TC/DTG (n=421). For those initiating TDF/3TC/DTG, 42% were female, and the median age was 35 years. Follow-up for both arms was impacted by COVID-19. Among those with an HIV RNA result, 85% of those starting TDF/3TC/DTG as an initial regimen were suppressed to below 50 copies/mL. For those switching to TDF/3TC/DTG while suppressed on a first-line regimen, 80% were female and the median age was 40 years. Among those with available viral load data, 96% had plasma HIV RNA level below 50 copies/mL. One participant developed a new integrase mutation T97A/T. The authors concluded that these preliminary data are supportive of the ongoing TDF/3TC/DTG rollout.

Clinical Pharmacology

Alternative modes of ART administration. Some patients have difficulty or are unable to swallow pills. Massih investigated the pharmacokinetics

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of ingesting fixed-dose elvitegravir/cobicistat/FTC/TAF dissolved in 120 mL of tap water in 12 volunteers without HIV infection (Abstract 447). They found that although the pharmacokinetic profiles did not meet the definition of equivalence, the observed differences were unlikely to be clinically meaningful. There were no complaints about the taste of the solution. The authors concluded that this may be a reasonable option for this subset of patients with substantial swallowing difficulties.

DeJesus and colleagues investigated administering ibalizumab via a slow IV push in people with and without HIV (Abstract 429). Ibalizumab is a long-acting attachment inhibitor administered by IV infusion indicated for MDR HIV. They found that this route of administration was bioequivalent to the standard infusion, and it may be a simpler option for administering the drug.

Urine tenofovir to predict viremia. Hermans and colleagues investigated the use of the point-of-care (POC) urine tenofovir assay to predict viremia among participants in a randomized, controlled trial of first-line ART regimens (Abstract 451). They found that a negative tenofovir result had a sensitivity of 69%, and 100% specificity for concomitant viremia. They also noted that participants with ongoing viremia and tenofovir detected were more likely to have drug resistance. The authors asserted that this assay may be useful by providing rapid insight into adherence.

Islatravir and LEN interactions. Zhang and colleagues evaluated possible pharmacokinetic interactions between islatravir and LEN, a novel investigational combination for long-acting ART, in 55 participants without HIV infection (Abstract 433). They found that drug concentrations for the 2 drugs met the predefined equivalency definition compared with administering the drugs separately. The authors concluded that there were no significant drug-drug interactions.

ART in severe renal disease. Weber and colleagues investigated the pharmacokinetics of a single oral dose of LEN in patients with severe renal dysfunction compared with those with normal renal function (Abstract 434). They found that LEN exposure was greater in those with severe renal impairment, including a 162% increase in the maximal concentration and an 84% increase in the area under the curve over 50 days. The authors did not believe that dose adjustment was necessary given available safety and pharmacokinetic data.

Molto and colleagues reported on the removal of doravirine by hemodialysis in 8 patients with HIV with end-stage renal disease (Abstract 435). They found an extraction coefficient of 35%; the concentration of doravirine in blood leaving the hemodialysis machine was 35% lower than blood entering the machine. Overall, dialysis reduced doravirine concentrations by 20%, but concentrations remained far above the target concentrations.

Drug-drug interactions involving contraceptives. Mngqibisa and colleagues presented data on the use of the emergency contraceptive levonorgestrel in women without HIV on rifampin-based tuberculosis therapy (Abstract 77). Rifampin is a potent inducer of cytochrome P450 and is expected to lower levonorgestrel concentrations. They enrolled 34 women who received levonorgestrel 3 mg, twice the normal dose. They compared the pharmacokinetics with a control group of women with HIV receiving DTG-based therapy, not on rifampin, who were enrolled in a different arm of the same trial. They found that the maximal concentration was 27% higher in the double-dose group, and the half-life was reduced by 57% leading to lower concentrations at 48 hours postdose. The authors noted that the efficacy of this contraceptive strategy is thought to be related to the maximal concentration and recommended this strategy to overcome the drug-drug interaction.

Chappelle and colleagues investigated a strategy to overcome a known drug-drug interaction whereby EFV lowers etonogestrel concentrations (Abstract 884). They randomly assigned 72 Ugandan women with HIV receiving EFV-based ART to receive a single etonogestrel implant or 2 implants. All women also received a copper intrauterine device for known effective contraception. The double

implant group achieved etonogestrel concentrations that were more than twice that of the single dose group, but still lower than historic controls. The double implant strategy reduced the odds of ovulation by 97% compared with the single implant group (2 vs 47 ovulation events, respectively). The authors recommended this strategy when using etonogestrel implants in women receiving EFV-based ART.

ART and the HIV reservoir/viral kinetics. Daar and colleagues presented data from ACTG A5354, looking at viral load in patients with acute and early HIV infection (Abstract 492). They grouped patients into categories based on their Fiebig stage. Group 1 consisted of 49 patients in Fiebig stage I and II, group 2 consisted of 30 patients with Fiebig stage III/IV, and group 3 consisted of 60 patients with Fiebig stage V. These patients started ART during the early HIV period, 98% with integrase strand transfer inhibitor (InSTI)-based regimens. Group 1 participants had higher rates of undetectable HIV viral load at week 24 than groups 2 and 3 (P=.005). By week 72, all groups reached undetectable viral load at similar rates. The study authors postulated that the shorter time to undetectable viral load in group 1 participants (those in Fiebig stages I and II, with only viral load or p24 antigen positivity but antibody negativity) may indicate benefit in starting ART right away, perhaps decreasing the viral reservoir.

Imaz and colleagues conducted a small, open-label, randomized, pilot clinical trial looking at viral kinetics of HIV in blood plasma, semen, and rectal fluid after initiation of ART (Abstract 495). They randomly assigned ART-naive cisgender men with an HIV viral load below 500,000 copies/mL to either a DTG plus 3TC arm or a TAF/FTC/BIC arm. Median HIV RNA was 4.56 $\log_{10}$ copies/mL in blood, 2.38 in serum, and 3.2 in rectal fluid. The authors did not observe any differences between treatment groups in viral load decline in any of the 3 body fluids. They did note that semen and rectal fluid viral load dropped to undetectable more quickly than in blood in both treatment arms; by day 28, more than 80% of individuals in both arms had achieved viral load below 20 copies/mL in semen and rectal fluid.

Jing and colleagues presented data on low-level viremia (LLV) and association with virologic failure (defined as a viral load of 1000 copies/mL or greater) in a Chinese cohort of more than 75,000 patients (Abstract 497). ART regimens were not discussed in the abstract. They found LLV to be quite common overall, in about 23.2% patients. LLV from 200 copies/mL to 399 copies/mL was associated with virologic failure (adjusted hazard ratio [aHR], 1.39; 95% CI, 1.27-1.53), and LLV from 400 copies/mL to 999 copies/mL was more strongly associated with virologic failure (aHR, 2.02; 95% CI, 1.87-2.18). LLV below 200 copies/mL was not associated with virologic failure (aHR, 0.90; 95% CI, 0.84-0.97). Conclusions are limited by not knowing ART regimens, but it suggests LLV above 200 copies/mL is predictive of virologic failure, whereas LLV below 200 copies/mL is more reassuring as it is not associated with virologic failure.

Data from participating in PEPFAR showed that linkage to care increased from 60% in 2016 to 90% in June 2020

The HIV Care Cascade and Disparities in Treatment Outcomes

New Population and Cohort-Based Data on the HIV Care Continuum

New population data across countries receiving support from PEPFAR (US President's Emergency Plan for AIDS Relief), the United States, and Spain all highlight continued challenges in the HIV care continuum, and investigators in Atlanta explored the impact of churn, or patients moving in and out of care, on outcomes. Data from quarterly reports from 41 countries participating in the PEPFAR program were aggregated to examine trends in linkage to HIV treatment over the past 5 years (Abstract 89). PEPFAR has supported the initiation of

same-day ART since 2015, and this analysis used a proxy for linkage to treatment—the number of people reported to be newly linked to treatment divided by the number of positive HIV tests in each quarter—to determine changes in linkage over time. In a dataset that included 99.3% of PEPFAR's HIV testing and treatment results, the investigators found that this proxy linkage percentage for people with HIV increased from 60% in March 2016 to 90% in June 2021. The increase was attributed to improved counseling during HIV testing events, implementation of same-day ART initiation, and expansion of capacity to provide linkage to treatment after testing. The analysis was limited by its use of aggregate data that could not determine length of time between diagnosis and the initiation of ART on an individual basis. In this context, data on linkage to care could represent those diagnosed many months ago, if not years ago, who are now presenting for care. Despite this reservation, the increase in proxy linkage over time highlights the importance of enhanced efforts to support linkage to care and the start of same-day ART.

Johnson Lyons and colleagues from the US Centers for Disease Control and Prevention (CDC) used data from the US National HIV Surveillance System (NHSS) in 2019 to assess the key goals of the Ending the HIV Epidemic in the United States (EHE) plan: linkage to care, defined as at least 1 CD4+ cell count or viral load test within 1 month of HIV diagnosis, and viral suppression to below 200 copies/mL within 6 months of diagnosis (Abstract 768). Across 45 jurisdictions, 77.8% of individuals newly diagnosed were linked to care, and 63.1% achieved viral suppression in 6 months. Unfortunately, only 5 jurisdictions met or exceeded the EHE target of 95% linked to care, and only 1 jurisdiction met the 95% target for viral suppression. The range of outcomes was also wide for both metrics, varying from below 50% for some areas to over 90% for others. There appeared to be more variation in outcomes for jurisdictions with fewer than 500 HIV diagnoses in 2019. These data demonstrate the continued challenges across the care continuum throughout the United States and highlight geographic disparities in outcomes.

The same NHSS dataset and care cascade outcomes were used by Mawokomatanda and colleagues at the CDC to focus on foreign-born persons in the United States, who account for 13% of the US population but 16% of new HIV diagnoses (Abstract 769). The authors found that linkage to care at 1 month was higher for people diagnosed with HIV who were foreign born (87.4%) than US born (81.3%). Similarly, viral suppression at 6 months after diagnosis was seen in 77.1% of foreign-born people with HIV and in 68.1% of US-born people with HIV. Statistically lower outcome metrics were noted in European-born persons for linkage to care and viral suppression, and in those older than 55 years of age, men who inject drugs, and those listed as living in an "unknown or other" population area for viral suppression. The investigators also examined the outcome of late diagnoses, defined as stage 3 at time of diagnosis, and found that 26% of foreign-born patients received a late-stage diagnosis, compared with 19% of US-born persons. The analysis underscores the challenges in access to HIV testing experienced by this population leading to delays in diagnosis, but is encouraging in demonstrating improved care cascade outcomes for foreign-born individuals with HIV. An analysis of the same dataset focusing on Hispanic or Latino persons with HIV found the same improved care cascade outcomes but higher frequency of late-stage diagnosis for foreign-born Hispanic or Latino persons than for US-born Hispanic or Latino persons. There were some variations by country of origin, with Mexican- and Central American-born persons having

Non-US-born people with HIV were more likely to receive late-stage diagnoses, but they experienced higher prevalence of linkage to care at 1 month and viral suppression than US-born people with HIV

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comparable care cascade outcomes to US-born persons (Abstract 899).

Alejos and colleagues also examined care cascade outcomes data within CoRIS (Cohort of the Spanish AIDS Research Network), which included 14,513 people with HIV receiving care between 2004 and 2020 at numerous hospital-based care centers across Spain (Abstract 890). Encouraging trends indicate improvements in timely diagnosis and linkage. Time from diagnosis to the initiation of ART decreased from more than 19 months in 2004 to less than 1 month in 2020 (*P* for trend <.001). Median CD4+ count at the initiation of ART increased from less than 250 cells/μL in 2004 to more than 350 cells/μL since 2012 (*P* for trend <.001). Two key care cascade metrics increased over the same observation period: linkage to care within 1 month of HIV diagnosis and viral suppression to below 200 copies/mL within 3 months of diagnosis. Linkage at 1 month increased from 41% to 83%, and viral suppression at 3 months increased from 4% to 41% (both *P*<.001). Viral suppression at 3 months was more likely for women, non-Spanish-born Europeans, Latin Americans, and those older than 50 years of age, and less likely for people using injection drugs, and those with CD4+ counts above 200 cells/μL. These encouraging improvements in care cascade outcomes across Spain demonstrate the impact of policy changes, such as the removal of CD4+ cell count–based initiation restrictions and the use of InSTI-based regimens, but it is unclear whether CoRIS is representative of the general population with HIV in Spain.

Gopalsamy and colleagues explored the impact of "churn," or the cycle of intermittent engagement in care experienced by some people with HIV, on care cascade and clinical outcomes (Abstract 772). Among 1303 people with HIV in newly establishing care in the Grady Infectious Disease Program in Atlanta between 2012 and 2017, 15.3% experienced churn, defined as a 1-year or more gap between either clinic visits or lab testing. Those returning to care were likely to have viral load measurements over 1500 copies/mL, but churn was not associated with increased odds of AIDS-defining illness, death, or loss to follow-up. Thus, in this clinic experience, the primary consequence of churn was the decreased prevalence of viral suppression and implied increased HIV transmission risk for the community.

Policy Changes and Programmatic Structures' Impact on the HIV Care Continuum

Decentralized ART distribution models, including community pharmacy-based refills, clinics with quick access or walk-in services, and community-based refill groups including peers or family members, can lower barriers to ART access for many people with HIV and may impact HIV care continuum outcomes. Onovo and colleagues compared the proportion of patients retained in care, defined as being alive and remaining on ART for at least 12 months after ART start, among 6 different decentralized ART distribution models serving 85,245 people with HIV in 2 Nigerian states (Abstract 936). Only 16% of patients experienced treatment interruption between October 2001 and December 2020, and overall retention probability was 62% at 36 months for the cohort. The median retention time in the community pharmacy-based ART refills program was 73 months, statistically significantly longer than median time in any of the other drug distribution models, which ranged from 14 to 49 months and included community-based refill clubs and expedited clinic and laboratory testing services. The observational nature of this study posed several challenges. Most notably, different implementation timeframes for the various distribution models likely impacted the analysis. Models that began enrolling patients later may have been more likely to show benefit because

Community pharmacy-based ART refills may support retention in care over time and may help to increase access to ART in the context of COVID-19 or other barriers to clinic-based care

of other factors impacting retention, such as the use of NNRTI-based regimens. The COVID-19 pandemic led to 5 of the 6 models expanding services to unstable patients during the last year of observation. Despite these limitations, the data presented demonstrate that community pharmacy-based ART refills may support retention in care over time in this real-world cohort.

Fennell and colleagues evaluated the impact of the expansion of access to free ART to noncitizen residents of Botswana in 2019 (Abstract 92). The investigators used data from an 18-site network to assess engagement in antenatal care, ART coverage, and adverse birth outcomes for pregnant citizens and noncitizens, comparing the time period before and after access to free ART was available for noncitizens. Of the 205,909 people delivering between August 2014 and September 2021, the proportion of noncitizens with unknown HIV status decreased from 6.3% to 1.3% after expansion of access to free ART. The proportion of noncitizens attending antenatal care increased from 79.3% to 87.3%, and among those with HIV, receipt of ART increased from 65.5% to 89.3%. Disparities in adverse birth outcomes between citizens and noncitizens decreased after free ART was provided for noncitizens. These data demonstrate that expanding access to ART to noncitizens can have substantial impacts on engagement in antenatal care and outcomes in addition to increasing HIV testing and treatment in this population.

Two abstracts examined the impact of AIDS Drug Assistance Program (ADAP) policies on HIV care continuum outcomes in the people with HIV served by the program. McManus and colleagues used HIV prevalence data from the CDC and aggregate ADAP State data to evaluate trends from 2008 to 2018 in ADAP utilization for key populations (Abstract 910). The percentage of people with HIV served by ADAP increased substantially, from 13.9% to 23.0% over the observation period, with similar trends across geographic regions. However, concerning disparities by race and ethnicity were observed. ADAP utilization for White people with HIV increased by 23% over the observation period, a statistically significant change from baseline, compared with increases seen for Black people with HIV of 11% and Hispanic people with HIV of 9%, neither of which were statistically significant from baseline. There was also a substantial increase in ADAP utilization for people with HIV of 13 to 24 years of age. These disparities in ADAP utilization bear further investigation as they are likely related to underlying disparities in access to care. Individual-level analyses, rather than State aggregated data, may be able to shed further light on differences by age and race/ethnicity.

Investigators from the NA-ACCORD (North American AIDS Cohort Collaboration of Research and Design) examined the impact of ADAP formularies on the care cascade outcomes of ART treatment and viral suppression (Abstract 771). They compared data on 14,415 people with HIV between 2014 and 2017 in states with open formularies that included all FDA-approved medications with those with otherwise restricted formularies. The proportion of people with HIV achieving timely ART initiation, defined as receipt of ART within 6 months of cohort enrollment, was 87% among people with HIV in open formulary states and 79% for states with restricted formularies, a statistically significant difference with adjustment for demographic, insurance, income, and geographic variation. The opposite was seen for achieving viral suppression, defined as a viral load of HIV RNA below 200 copies/mL within 1 year of ART initiation: 86% of people with HIV in open formulary states and 90% of those with HIV in restricted formulary states achieved viral suppression, but this difference did not reach statistical significance. These data suggest that the initiation of ART may be timelier in states with an open formulary, although the impact on viral suppression, the final step of the care cascade, is unclear. The analysis was limited by the heterogeneity of the definition of restricted formulary and inability to account for other ADAP program characteristics, such as eligibility thresholds, that served as structural barriers to care in this context.

Medical and Structural Interventions to Improve the HIV Care Continuum

Mpoudi-Etame and colleagues presented long-term outcomes from the fourth year of follow-up within the NAMSAL (New Antiretroviral and Monitoring

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Strategies in HIV-Infected Adults in Low-Income Countries) trial,[6] which randomly assigned more than 600 people with HIV initiating ART in Cameroon to first-line treatment with a DTG-based regimen or an EFV 400 mg–based regimen (Abstract 493). Viral suppression, defined as HIV plasma RNA level below 50 copies/mL at week 192, differed between the EFV arm (61.7%) and the DTG arm (69%) in the ITT analysis, but did not reach statistical significance (P=.057). A per protocol analysis showed 65.7% viral suppression in the EFV arm and 74.8% in the DTG arm, a difference that did reach statistical significance (P=.035). The investigators also tracked body weight gain over the 4 years of follow-up and noted more weight gain in the DTG arm and more substantial weight gain among women. These data suggest that the transition to DTG-based regimens in low- and middle-income countries (LMICs) may lead to improvements in viral suppression. However, considering co-occurring metabolic and cardiovascular risk for people with HIV, the prevalence of weight gain associated with DTG-based regimens is of concern.

A transition to DTG-based regimens in low- and middle-income countries may lead to improvements in viral suppression but was also associated with weight gain, particularly for women

Investigators from CoRECT (Cooperative Re-Engagement Controlled Trial) presented results of their multisite prospective randomized control trial conducted in Massachusetts, Connecticut, and the city of Philadelphia (Abstract 94). They compared standard of care with a data to care approach that used HIV surveillance data to identify and reengage people recently out of care. Researchers defined newly out of care as those who received HIV care within the last 12 months but then either: a) did not have a CD4 or HIV plasma RNA level test for over 6 months and/or b) missed appointments or had no clinic visit for 6 months. Primary outcomes were reengagement at 90 days, retention in care at 12 months, viral suppression at 12 months, and durable viral suppression at 18 months. The intervention arm achieved 54.9% reengagement compared with 42.1% in the standard of care arm (P<.0001), and improvements in retention were 51.2% in the intervention arm and 46.5% in the standard of care arm (P=.04). However, they did not find statistical differences in durable viral suppression, including in several sensitivity analyses. It is concerning that this intervention, which increased engagement in care and retention, did not lead to improvements in viral suppression over time.

Randomized control trials testing interventions to address structural barriers to care that impact the HIV care continuum are challenging to conduct, and the 2022 Conference on Retroviruses and Opportunistic Infections provided several examples of studies that tackled this issue with innovative study design. Solomon and colleagues assessed the efficacy of nonmonetary incentives in improving HIV treatment outcomes, including viral suppression, among men who have sex with men (MSM) and people who inject drugs (PWID) in India (Abstract 93). A pair-matched cluster design created 8 pairs from 16 participating integrated care centers that provide nondiscriminatory services for the 2 key populations, but do not provide ART. Pairs were matched on target population, estimated population size, HIV prevalence, viral suppression metrics, and the percentage of viremic persons in the community. The investigators established cohorts of 150 participants with HIV at each site and randomly assigned 8 clusters to standard of care and 8 to the intervention. The intervention offered nonmonetary incentives of between US $1.30 and $7.00 for attendance at visits for follow-up pre-ART initiation, ART initiation, motivational interviewing, and timely ART refills. The planned primary outcome was viral suppression to below 150 copies/mL at 24 months, but the initiation of the COVID-19 national lockdown in March 2020 led to a revision of the primary outcome to plasma HIV RNA level below 150 copies/mL at 12 months. Most participants in the intervention

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arm earned at least 1 incentive, but the primary outcome of percentage achieving viral suppression, as measured by an adjusted prevalence ratio of 1.22 (95% CI, 0.63-2.34) in the intervention arm compared with the control arm, did not differ significantly. Statistically significant differences were also not noted when the outcomes were stratified by key population (MSM or PWID), nor in a sensitivity analysis including only ART-naive participants. The lack of impact of the intervention, particularly in the context of low prevalence of viral suppression overall, which was 65% in the intervention cohort and 46% in the control cohort at 12 months, highlights the need for more effective strategies to support viral suppression, particularly for key populations.

A multisectoral agricultural intervention was not associated with increased viral suppression when compared with standard of care, but was linked to marked differences in food insecurity and other health-associated outcomes

In another cluster randomized trial, Cohen and colleagues addressed food insecurity in Kenya by randomly assigning 8 pairs of health facilities to a climate adaptive intervention that included human-powered water pumps, bank loans for farming commodities, and training in sustainable agriculture, financial literacy, and agribusiness (Abstract 891). Their primary outcome, absolute change from baseline at 24 months in viral suppression to less than 200 copies/mL among the 720 individual participants, improved in both arms from 82% to 86% at baseline to 95% at 24 months, but did not differ statistically between groups. However, compared with the control arm, the intervention arm participants had substantial improvements in food security, social support, and stigma scores at 12 months, which were sustained at 24 months. The investigators noted that widespread test-and-treat policies were launched during the study period. Despite the intervention's lack of effect on the primary outcome, the marked differences in food insecurity and other health-associated outcomes speak to its broad impact on participants.

Wohlfeiler and colleagues conducted a cluster randomized controlled trial of a web portal and mobile app that parsed health record data to provide actionable alerts for clinicians in 20 healthcare centers caring for almost 16,000 people with HIV in the southern United States (Abstract 908). The intervention provided care engagement alerts to clinicians for the following criteria: no visits for 4 months with none scheduled in the next 2 months; single visit in the prior 12 months with missed visit and none scheduled in the next 2 months; 2 sequential missed visits and none scheduled in the next 7 days; and an HIV viral load above 1000 copies/mL over 3 months ago without a more recent viral load under 20 copies/mL and no visit scheduled in the next 7 days. The investigators noted that changes were made during the study period in these parameters because scheduling within 7 days was deemed impractical, and that a viral load threshold of below 50 copies/mL was more consistent with standard of care. Although differences were seen in the number of return visits after alerts between the intervention and control arms, none of the tests for statistical significance presented differed between arms. The investigators also noted challenges in incorporating the study intervention into existing retention in care efforts, competing demands on staff time, and the impact of the COVID-19 pandemic and extreme weather events on clinic operations.

Impact of the COVID-19 Pandemic on HIV Care

Interventions and Disruptions in the HIV Care Continuum During the COVID-19 Pandemic

Assessment of the impact of the COVID-19 pandemic on the HIV care continuum has begun, and COVID-19–related disruptions in the HIV care continuum were examined by Castel and colleagues in a 15-site network of HIV treatment clinics in

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Washington, DC, a metropolitan area severely impacted by both the HIV and COVID-19 epidemics (Abstract 940). Care continuum metrics of care engagement—defined as at least 1 clinic visit, plasma HIV RNA measurement or CD4+ cell count measurement on ART based on prescription refill data, and viral suppression to HIV RNA levels below 200 copies/mL—were compared for 8288 people with HIV in 2 timeframes: prepandemic (January 1, 2019-February 28, 2020) and peripandemic (March 1, 2020-September 1, 2021). Significant declines were seen in all 3 metrics: care engagement decreased from 71.1% to 62.7%, on ART decreased slightly from 92.7% to 91.0%, and viral suppression decreased from 69.6% to 61.7% (all *P* values for difference <.001). A subsample of people with HIV (n=801) participated in a survey of the self-reported impact of COVID-19, and 20% of participants reported challenges in making appointments for HIV care. This analysis demonstrates setbacks in HIV care continuum progress during the first year and a half of the COVID-19 pandemic in a large urban cohort and highlights the need for increased care engagement efforts.

Chaudhuri and colleagues also compared HIV care outcomes between a pre-COVID-19 period, March 2019 to February 2020, and during the COVID-19 pandemic, March 2020 to February 2021, for 9740 people with HIV receiving care in a New York City–based clinic network (Abstract 946). They noted that although the prevalence of viral suppression, defined as a plasma HIV RNA level below 200 copies/mL on last check, remained stable from 87.9% pre-COVID-19 to 90.7% during COVID-19, 18% of the cohort did not have HIV plasma RNA levels measured during the first 12 months of the COVID-19 pandemic, and 15% did not have laboratory testing or clinic visits. In adjusted analysis, predictors of the combined outcome of viral nonsuppression or absence of HIV plasma RNA measurement included male sex, transgender individuals, those under 50 years of age, heterosexual men, and PWID. Investigators also noted that, although clinic visits and lab checks decreased during COVID-19, ART prescription rates remained consistent. These data highlight how adjustment for viral load measurement is important in these analyses, and the need for further care engagement efforts during the pandemic, particularly for marginalized populations.

Masters and colleagues examined the impact of telehealth on HIV care quality indicators before and during the COVID-19 pandemic in 2 Chicago clinics, 1 academic-based and 1 community-based (Abstract 937). Indicators were assessed during 4 overlapping 15-month periods between January 2019 and September 2021, and 64,447 people with HIV were included in the analysis. Despite the rapid adoption of telehealth visits, the proportion of patients with a clinician encounter in the last 8 months decreased from 89% in the first timeframe to 68% in the final, and all 3 time periods that occurred during the pandemic were statistically significantly lower than the first prepandemic measurement. Significant decreases were also seen in other indicators, including testing for plasma HIV RNA, blood pressure, A1c measurement, and mammograms and STI screening. Although changes were not noted over time in viral suppression to less than 50 HIV RNA copies/mL, nor in diabetes or blood pressure control, it is possible that these indicators were falsely elevated during the pandemic because of lack of measurements, for which no adjustments could be made in the analysis. The data demonstrate worsening across several HIV care metrics, despite transition to telehealth.

Cross-sectional self-reported care engagement data from 773 people with HIV enrolled in the C3PNO (Collaborating Consortium of Cohorts Producing NIDA Opportunities) study were used by Lesko and colleagues to examine predictors of missing HIV care visits or ART doses (Abstract 945). Thirteen percent of respondents reported missing a medical visit in the past month, and 19% had missed at least 1 ART dose in the past week. Investigators assessed reasons for missed ART doses, and 21% of respondents reported they were unable to refill ART or were concerned about entering a pharmacy because of the risk of COVID-19. After adjustments for demographic, structural, and clinical predictors, smoking was associated with missing

visits, and male sex, low reported resiliency, cocaine use, cannabis use, and disruptions to substance use treatment were all associated with missed ART doses. These data suggest that an increased focus on care engagement for those with substance use disorder could support the HIV care continuum during the pandemic, but do not reveal whether these predictors are exacerbated by COVID-19.

Spinelli and colleagues reported on the impact of the COVID-19 pandemic on HIV care cascade outcomes at a safety net clinic in San Francisco, California (Abstract 888). They noted an initial drop in viral suppression, defined as a plasma HIV RNA level below 200 copies/mL, from a mean of 84% pre-COVID-19 to 81% in April 2020. The clinic implemented various simultaneous engagement in care strategies at the end of March 2020, including phone outreach, resumption of in-person visits, expansion of the permanent housing program, a shelter-in-place hotel room program, and an expansion of POP-UP (Positive Health Onsite Program for Unstably Housed Populations), an existing program for people with unstable housing and virologic nonsuppression with dedicated staff, walk-in clinic visits, and incentives. Telehealth services increased during shelter-in-place and remained at 10% of visits in April 2021. The investigators found that outreach workers contacted 91% of all people with HIV served by the clinic, and that 7.3% of people with HIV were in care at other sites, reducing the true loss to follow-up rate to 2.8 per 100 person-years, which was comparable to the rate prior to COVID-19. Investigators also found that the proportion achieving viral suppression increased 1.05-fold per month (95% CI, 1.01-1.08) from April 2020 to April 2021; it reached 90%. Based on the data presented, it is unclear if this analysis was adjusted for number of plasma HIV RNA measurements, which could falsely elevate estimates of viral suppression. Despite this limitation, the clinic's experience suggests that the multicomponent strategies implemented reduced barriers to achievement of virologic suppression for people with HIV and continued to have an impact in the second year of the COVID-19 pandemic.

A multicomponent strategy for care engagement, including housing support and expedited visits, reduced barriers to achievement of virologic suppression for PWH during the COVID-19 pandemic

HIV Resistance

Epidemiology of HIV Resistance

Garcia presented resistance prevalence data on newly diagnosed ART-naive patients in southern Europe from 2018 through 2021 (Abstract 516). They studied more than 2700 patients; median viral load was 108,006 copies/mL, 56.3% had subtype B, and prior pre-exposure prophylaxis (PrEP) use was not mentioned. The overall prevalence of nucleoside analogue reverse transcriptase inhibitor (nRTI)-resistance mutations was 3.73%; 0.85% had M184V, 0.18% had M184I, 0.04% had K65R, and 2.66% had presence of other thymidine analogue mutations. The overall prevalence of InSTI-resistance mutations was very low at 0.23%; they found 1 for each of the following mutations: T66I, T66A, E138T, E138K, E92Q, and R263K. The prevalence of clinically relevant resistance, which they defined as a score of 3 or more by Stanford interpretation, was 2.42% for InSTIs and 1.76% for nRTIs. The investigators found that 0.89% had resistance to either TDF or TAF, and 1.15% had resistance to either 3TC or FTC. There were higher rates of resistance to first-generation InSTIs raltegravir and elvitegravir (about 2.3%), but only 0.18% to BIC and 0.18% to DTG. Based on these prevalence numbers, there were low rates of higher-generation InSTI resistance, and it is unlikely these mutations would be of consequence to newly diagnosed patients placed on more modern regimens.

Novitsky and colleagues presented on the epidemiology of transmitted drug resistance in newly

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diagnosed patients with HIV from 2004 to 2020 in Rhode Island (Abstract 517). They looked at data from more than 1100 patients and found that transmitted drug resistance to any drug increased from 8% in 2004 to 26% in 2020 (Mann-Kendall statistic, 0.47; 95% CI, 0.16-0.68). Of all drug classes, NNRTI-associated resistance mutations increased most dramatically, from 5% in 2004 to 18% in 2020, most commonly K103N. Drug mutations associated with nRTIs increased from 2% in 2004 to about 8% in 2020, with 0.5% with M184V/I, and no instances of K65R transmitted drug resistance (TDR). PI-associated mutations remained low, from below 2% in the mid-2000s to an estimated 2% to 3% in 2019 to 2020. The investigators did not find major InSTI mutations, although this information was limited to 49 samples. TDR to 2 or more classes was uncommon. Overall, the study found increasing TDR rates over the study period from 2004 to 2020, mostly driven by an increase in NNRTI-associated resistance mutations, with no substantial evidence of drug resistance mutations (DRMs) to components of first-line regimens.

Hu and colleagues' findings suggest a mechanism for more clinical failure with L74I-containing virus; although the presence of this mutation itself does not confer resistance to cabotegravir, when combined with other integrase mutations, it allows for improved replication capacity, enhancing cabotegravir resistance conferred by other integrase mutations

Resistance Patterns of Existing Agents (Including Long-Acting Agents)

Hu and colleagues examined the effect of the L74I mutation in integrase on viral replication (Abstract 506). L74I in A6 subtype virus was associated with higher rates of virologic failure in trials of CAB-LA and RPV. The investigators found that presence of L74I in subtype A6 virus did not affect susceptibility to CAB. However, virus with L74I outcompeted wild-type L74 virus in growth competition assays, indicating greater viral fitness of L74I-containing virus. When L74I was combined with other mutations causing resistance to InSTIs, specifically either G118R, G140R, Q148R, or R263K, this virus had significantly higher replication capacity than wild-type L74 virus with integrase resistance mutations. There was no difference in replication capacity when L74I was combined with Q148H or Q148K. L74I when combined with N155H lowered replication capacity compared with wild-type L74 virus with N155H. Those viruses containing G140R and Q148R were unable to replicate to assess capacity adequately. The results slightly differed in the presence or absence of CAB. When L74I was combined with other InSTI-associated mutations, either G118R, G140R, G148H, G148R, or R263K in the absence of CAB, this virus had significantly higher replication capacity than wild-type L74 combined with InSTI-associated mutations. In the presence of 2 nM of CAB, only L74I combined with either G118R or G140R had increased replication capacity. The L74I combinations with G148H, G148R, or R263K no longer had statistically significantly increased replication capacity in the presence of 2 nM of CAB. In the presence of 4 nM of CAB, these findings were similar, except L74I and R263K virus had higher replication capacity than wild-type L74 and R263K. These findings suggest a mechanism for more clinical failure with L74I-containing virus; although the presence of this mutation itself does not confer resistance to CAB, when combined with other integrase mutations, it allows for improved replication capacity enhancing CAB resistance conferred by other integrase mutations. The effect is not equal for all integrase mutations in the presence of CAB.

Dekker and colleagues examined mutations in the 3'-polypurine tract (3'PPT) that may confer DTG resistance and explored the mechanism of action (different from integrase mutations) (Abstract 507). They cultured 3'PPT variants in the presence of DTG

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and noted that certain 3'PPT mutations that conferred DTG resistance reduced viral fitness but actually improved replication activity. The 3'PPT mutations are able to work around integrase inhibition by triggering replication that is independent of the process of integration and therefore still able to replicate in the presence of DTG-inhibiting integration. Prior studies had shown that 3'PPT mutated virus may need an external trigger (eg, HTLV-1 Tax protein[7]), and it is not quite known what the clinical implications are for these in vitro findings. Similarly, van Kampen and colleagues examined the 3'PPT region in patients with HIV in Brazil in whom ART with DTG was failing and found 3'PPT mutations in 6 of 45 of these patients (Abstract 512). Further research is ongoing to determine the effect of these mutations on fitness, replication, and InSTI susceptibility.

Boyce and colleagues examined samples of pregnant women from IMPAACT 2010 (Evaluating the Efficacy and Safety of Dolutegravir-Containing Versus Efavirenz-Containing Antiretroviral Therapy Regimens in HIV-1-Infected Pregnant Women and Their Infants) who had confirmed virologic failure on ART and looked for DRMs (Abstract 509). The rates of virologic failure and presence of drug resistance were lower (meeting statistical significance, with $P<.05$) in the DTG arms than in the EFV arms. In the DTG plus TDF/FTC group, 1.9% of participants had drug resistance at virologic failure compared with 6.2% in the EFV/TDF/FTC arm ($P=.023$). Furthermore, 0.9% of participants in the DTG plus TAF/FTC group had resistance ($P=.0032$ compared with EFV arm). The investigators were able to genotype 35 samples of 42 virologic failures and found 54% (19 of 35) of these samples had drug resistance. Seventy-nine percent of samples with drug resistance (15 of 19) had resistance at the time of entering the study, and 47% (9 of 19) also had new mutations at the time of virologic failure. In the women who had drug resistance at the time of virologic failure, 54% in the EFV arm had new EFV-associated mutations (K103N, V106M, and P225H, along with some additional nRTI mutations). One of 6 women (17%) who had drug resistance at time of virologic failure had major InSTI-associated mutations, including N155H, L74I, S147G, and S230R. The authors concluded that those in the EFV-based arm were more likely to have virologic failure and develop new DRMs at the time of virologic failure than those in the DTG arms.

DTG plus darunavir/cobicistat (DRV/c) is often used by patients with MDR-HIV infection. This regimen was studied in an open-label multicenter randomized trial by Ramón Santos and colleagues to assess efficacy (Abstract 510). They enrolled adults with HIV on a 3-drug ART regimen who had been virally suppressed with HIV RNA level below 50 copies/mL for at least 6 months prior to random assignment. Participants had to have resistance against 2 drug classes but not the presence of resistance to an InSTI or DRV. Results were presented from 45 patients enrolled in the investigational arm to switch to DTG plus DRV/c, and 44 patients enrolled in the control group to continue their current regimen. The primary outcome of HIV RNA level below 50 copies/mL at week 48 was similar between both groups, with a rate of 95.6% in the investigational group versus 90.9% in the control group (log rank $P=.392$). No virologic failures were observed in the investigational group, compared with 2 in the control group, but this difference was not statistically significant ($P=.147$). Ultimately, the authors concluded that dual therapy with DTG plus DRV/c was an effective option for patients with MDR-HIV without InSTI and DRV mutations.

Dual therapy with DTG plus DRV/c was an effective option for patients with MDR-HIV without InSTI and DRV mutations

Allesandri-Gradt presented in vitro susceptibility of HIV-1 non-M groups (O, N, and P) to ibalizumab (Abstract 501). They found 100% of the O and N groups tested were susceptible to ibalizumab, and group P was naturally resistant. Their work suggests that further testing on large panels of virus is needed but hints that ibalizumab could be used as treatment for HIV-1 groups O and N.

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Resistance Patterns of Novel Agents

Margot and colleagues presented data on LEN susceptibility and treatment response in treatment-experienced patients with MDR-HIV from the CAPELLA study (Abstract 508). LEN is a capsid inhibitor that interferes in various stages of the viral life cycle, including nuclear transport of the capsid, viral assembly and release, and capsid assembly. They evaluated whether LEN susceptibility was affected by the presence of entry inhibitor mutations to maraviroc, ibalizumab, enfuvirtide, and fostemsavir. In the 62 patients studied with information about entry inhibitor mutations, resistance to entry inhibitors was widespread, with 67.2% of isolates resistant to maraviroc, 31.5% to fostemsavir, 29.3% to ibalizumab, and 8.6% to enfuvirtide. In these isolates, there was no change in LEN susceptibility despite the level of resistance. Changes in the envelope or tropism did not affect LEN susceptibility. Treatment outcomes at week 26 did not differ in those patients on LEN with entry inhibitor mutations compared with those without mutations. The authors concluded that there was no association between resistance to entry inhibitors and susceptibility or clinical response to LEN, and this supports the use of LEN in treatment-experienced patients.

Montaner and colleagues examined the bNAb combination of 3BNC117 and 10-1074 (Abstract 503). They screened 61 patients with HIV who were virally suppressed with HIV RNA level below 20 copies/mL and who had a CD4+ count of at least 450 cells/μL. Twenty-four percent of patients had reduced susceptibility to 3BNC117, and 31% had reduced susceptibility to 10-1074. Fifty-six percent of the patients screened had virus that was susceptible to both bNAbs. The investigators did not find a correlation between susceptibility to either bNAb ($r=.10$). This indicates that there is presence of reduced susceptibility in circulating virus, and caution is needed when using a combination of 2 bNAbs as treatment.

Zacharopoulou and colleagues presented data on 173 patients with primary HIV infection in the United Kingdom who had been on ART for at least 1 year with an undetectable viral load (Abstract 505). Of these patients, 38.7% had resistance to either or both bNAbs. Resistance to 10-1074 was more common; it was present in 66% of the samples with resistance mutations. Interestingly, there was evidence for transmitted resistance and in-host evolution. The authors concluded that screening before administration of bNAbs was key to ensuring that patients' virus would be susceptible, as nearly 40% of this cohort had some baseline resistance to the bNAbs. Pahus and colleagues looked at concordance between a monoclonal antibody assay and 2 genotypic prediction algorithms for sensitivity of 2 bNAbs, 10-1074 and 3BNC117 (Abstract 504). The 3 methods were concordant in predicting susceptibility to 3BNC117 52% of the time, and susceptibility to 10-1074 79% of the time.

Hoffman and colleagues' findings highlight the variability of proviral genotyping with its limitations in interpretation and usefulness in clinical decision making

Smith and colleagues presented data on susceptibility of HIV-2 to GSK2838232, a maturation inhibitor that is being studied in phase II trials for treatment for HIV-1 (Abstract 500). They found HIV-2 was intrinsically resistant to this agent, and it retained little activity against HIV-2, suggesting that GSK283 could not be used for treatment of HIV-2 infection.

Clinical Implications of Resistance Testing

Hoffman and colleagues examined the temporal variability of proviral genotype sequencing in patients with MDR-HIV who had been virally suppressed on an ART regimen (Abstract 513). They examined proviral genotyping from samples from 2017 and 2020 in patients who had evidence of mutations associated with resistance to at least 3 classes of ART. These patients had sustained viral suppression with no treatment interruptions or viremia; the

median time of viral suppression was 9.0 years. Using a cutoff of above 15%, proviral genotyping was able to find 63% of baseline resistance mutations, as well as 7% of previously undetected resistance mutations. Interestingly, less than 40% of the mutations were found at both timepoints. Using cutoffs of above 1% yielded more favorable numbers, with proviral genotyping finding 76% of baseline mutations and 19% of previously undetected resistance mutations. With the above 1% cutoffs, less than 50% of the mutations were found at both timepoints. Twenty-three percent of patients had higher rates of detected resistance-associated mutations (RAMs) in 2020 than in 2017, whereas 50% of patients had lower rates of detected RAMs in 2020 than in 2017, and 27% of patients had similar rates at the 2 timepoints. Detection rates were not associated with level of proviral DNA, time of virologic suppression, or ART regimen. Rates were numerically increased in those patients with CD4+ count nadir below 50 cells/μL and CD4+ count below 750 cells/μL in 2020, but the differences did not reach statistical significance. This highlights the variability of proviral genotyping, with its limitations in interpretation and usefulness in clinical decision making.

Gaitan and colleagues examined whether proviral genotyping from samples before initiation of ART would detect resistance mutations that could impact clinical outcomes (Abstract 514). Of note, both tests were congruent for major resistance mutations except for 2 K103N mutations that are found only in proviral DNA. Eleven InSTI-associated resistance mutations (using a cutoff of >2%) were found in HIV proviral genotyping. However, mutations found in proviral DNA with a cutoff of greater than 2% were not associated with virologic failure with a follow-up period of about 25 months. Ultimately, the proviral genotype mutations observed did not predict virologic failure, and RNA genotyping was congruent with proviral DNA genotyping for major resistance mutations. However, the study authors recommended caution in using NNRTI-based regimens for initial therapy, as major resistance mutations (eg, K103N) were not found on RNA genotyping but found on proviral DNA genotyping, which may lead to eventual resistance.

Advances in Treatment of Hepatitis C

Epidemiology of Hepatitis C Virus

Hudson and colleagues presented data on HIV and hepatitis C virus (HCV) infection incidence rates in PWID from Kanawha County, West Virginia, which includes the state capital of Charleston (Abstract 536). They observed a very high rate of HCV seropositivity at 94% in PWID diagnosed with HIV. HCV diagnosis was found before HIV diagnosis in 82% of patients, with a median interval of 46 months, or almost 4 years (interquartile range [IQR], 29-71). They concluded that HCV infection is a high-risk predictor of subsequent HIV infection, and HIV testing and PrEP services should be scaled up in these populations. Ma and colleagues conducted a cross-sectional study looking at HCV infection rates in transgender women with HIV in the Centers for AIDS Research (CFAR) Network of Integrated Clinical Systems (CNICS) cohort from 2014 through March 2021 (Abstract 537). They observed higher rates of HCV infection in transgender women than cisgender men (adjusted odds ratio [aOR], 1.70; $P<.01$), and transgender women were more likely to be HCV viremic (aOR, 1.54; $P=.03$). When controlling for injection drug use, transgender women still had higher rates of HCV infection than cisgender men (aOR, 1.61; $P=.01$). This study demonstrates that transgender women remain at high risk for HCV acquisition even in absence of injection drug use and should receive frequent screening. Hung presented data about HCV elimination in people with HIV in Taiwan from 2013 to 2021, where patients with HIV were screened for HCV and then received treatment (Abstract 538). They observed a 78% decrease in prevalence of HCV viremia from 2013 to 2021, and an 84.6% decrease in the incidence rate of viremia from a peak of 131.6 per 1000 person-years of follow-up in 2011 to 20.3 per 1000 person-years of follow-up in 2021. They observed a 67.9% decrease in the incidence rate of HCV seroconversion from 2013 to 2021. This is in contrast to HCV rates in MSM in Germany presented by Ingiliz and colleagues, where the researchers examined the effect of COVID-19 on HCV elimination efforts (Abstract

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539). They found no change in HCV infection incidence through 2019 despite the use of direct-acting antivirals (DAAs), but they saw a decrease in 2020 and 2021, which they postulated was secondary to behavioral changes due to the COVID-19 pandemic.

Sun and colleagues examined the impact of an alternative HCV screening method using the HCV core antigen (HCVcAg) (Abstract 541). Advantages of HCVcAg screening include a lower cost of testing than HCV RNA screening and earlier detection of infections than HCV antibody testing. HCVcAg can be detected 1.5 months before HCV antibody is detected in the serum and HCVcAg can be detected 1 to 2 days after HCV RNA is found in serum. The investigators tested blood samples from 1639 participants including persons at high-risk and at low-risk. Of the blood samples tested, 3.8% were positive for HCV RNA, and 87.1% of these samples tested positive for HCVcAg (sensitivity). Also, 12.9% of the patients with a positive HCV RNA had a negative HCVcAg assay with a median HCV RNA of 3.2 $\log_{10}$ IU/mL. In the negative HCV RNA blood samples, 99.4% also tested negative for the HCVcAg (specificity). Given the prevalence of 3.8%, they calculated a positive predictive value of 85.7% and a negative predictive value of 99.5%. The authors concluded that HCVcAg has high specificity but decreased sensitivity, especially in those with a low HCV viral load. However, this could remain a viable screening tool in low-resource settings that are unable to use HCV viral loads as screening, and could increase detection when used with HCV antibody testing.

HCVcAg could remain a viable screening tool in low-resource settings that are unable to use HCV viral loads as screening, and could increase detection when used with HCV antibody testing

Treatment of HCV

Menétrey presented final data from Storm-C-1 (Strategic Transformation of the Market of HCV Treatments), an open-label, single-arm, phase II/III clinical trial in Malaysia and Thailand on the use of ravidasvir,[8] which is a pan-genotypic nonstructural protein 5A inhibitor developed through the Drugs for Neglected Diseases initiative (DNDi) for use in LMICs (Abstract 528). This trial enrolled 603 patients with hepatitis C who were between the ages of 18 and 69 years, either without cirrhosis or with Child-Turcotte-Pugh class A cirrhosis, and gave them ravidasvir plus sofosbuvir (SOF) for 12 weeks (or 24 weeks to those with cirrhosis) and measured sustained virologic response (SVR) 12 weeks after treatment ended (SVR12). Forty-nine percent of patients had genotype 3 infection, and 40% had either genotype 1a or 1b infection. Thirty-nine percent of patients had compensated cirrhosis, and 32% had coinfection with HIV. The overall rate of SVR12 was 96.8% and remained above 96% in patients with cirrhosis, HIV coinfection, and prior treatment with interferon alfa. There appeared to be slightly lower rates of SVR12 in the genotype 6 group, with SVR12 achieved in 88.5% of the population, but there were only 61 patients total. There was 1 serious adverse event (acute kidney injury) possibly attributed to SOF. The study authors concluded that the combination of ravidasvir and SOF was safe and effective in achieving SVR12 even in complex populations (ie, patients with cirrhosis, HIV coinfection).

Ravidasvir and SOF were safe and effective in achieving SVR12 even in complex populations (eg, patients with cirrhosis, HIV-coinfection)

Martín-Carbonero and colleagues examined the effectiveness of a pangenotypic combination of SOF

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plus velpatasvir plus voxilaprevir (SOF+VEL+VOX) in patients with HIV and HCV coinfection in whom previous HCV treatment with other DAAs failed (Abstract 529). They studied 56 patients in Spain with a median age of 51.9 years and an 18% rate of cirrhosis. Seventy-three percent of patients had an undetectable HIV viral load at time of enrollment (<50 copies/mL). Sixty-eight percent of patients had genotype 1 HCV, 13% had genotype 3, and 16% had genotype 4. The group was mostly treatment experienced with exposure to 1 prior regimen in 77% of patients, 2 prior regimens in 16% of patients, and 3 or more in 8% of patients. Most patients had been treated with a combination of SOF and ledipasvir (50% of participants). Nine percent of patients had been previously treated with glecaprevir/pibrentasvir, and 9% had been previously treated with SOF and daclatasvir. The investigators observed an 80% rate of SVR12 in their ITT group, and a 96% rate of SVR12 in their per protocol group. They observed a 90% rate of SVR12 in patients with cirrhosis in the ITT and per protocol groups. They did not observe a significant change in rates of SVR12 among different genotypes. The study authors concluded a regimen of SOF+VEL+VOX was effective in achieving SVR12 in patients with HIV and HCV coinfection in whom previous DAA regimens had failed, regardless of genotype or presence of cirrhosis.

Sowah and colleagues examined the association of adherence with SVR12 in the ACTG A5360 MINMON (Minimal Monitoring) trial, the results of which were recently published showing that minimal monitoring of HCV treatment with a 12-week course of SOF plus VEL was safe and effective in achieving SVR12 (Abstract 530).[9] Patients enrolled were HCV treatment naive; those with decompensated cirrhosis were excluded. Ninety-five percent of patients overall achieved SVR12 with 12 weeks of SOF plus VEL. Adherence at week 4 was highly associated with SVR, with 96% of patients reporting taking all their doses at week 4 achieving SVR12 (P<.01). In contrast, SVR was achieved in 77% of those who reported not taking all their doses at week 4. Adherence at week 24 and overall adherence were not associated with SVR12. Age under 30 years was highly associated with not taking all doses by week 4 (OR, 7 in a multivariate model). The study authors concluded that for HCV programs using the minimal monitoring approach, identifying those patients with suboptimal adherence at 4 weeks would be important, as this was predictive of achieving SVR12. More resources can be utilized to help this population, as well as younger patients, with adherence to increase the rate of SVR.

HCV Outcomes

Berenguer and colleagues presented data looking at the composite outcome of decompensation, hepatocellular carcinoma, or death in patients with HIV and HCV coinfection with advanced fibrosis (F3) or cirrhosis (F4) treated with DAA agents (Abstract 531). They examined 1300 patients (median age, 52 years); almost all patients (98%) were on ART, and 94% of patients had undetectable HIV viral load. The investigators observed increased rates of clinical progression in patients who had decompensated cirrhosis at baseline (HR, 2.25; P=.029) and male sex (HR, 1.99; P=.011). There was also an association with age (HR, 1.06; P=.001) and liver stiffness per 4-kPa increase (HR, 1.03; P<.001), but these effects were less pronounced than the prior variables mentioned. Higher serum albumin level and change in liver stiffness per 10% decrease at 1 year after therapy were associated with decreased risk of clinical progression (HR, 0.59; P<.001; and HR, 0.84; P<.001, respectively). These metrics can be used to develop scores to predict groups at high risk of progression to decompensation, hepatocellular carcinoma, or death in HIV and HCV coinfected patients who have been treated.

Requena and colleagues compared mortality rates in patients with HIV and HCV coinfection whose HCV infection was treated with DAAs and patients with HIV monoinfection (Abstract 532). There were low rates of cirrhosis (8.7%) in the HIV and HCV coinfection group, and the investigators used Poisson models controlling for age, AIDS status, and CD4+ count nadir, along with other variables. There were higher rates of death up to 36 months in the coinfected group, with an incidence rate ratio (IRR) of 1.59 (95% CI, 0.97-2.62) compared with monoinfected patients. This effect was most pronounced

from 18 to 36 months, when the risk of death for monoinfected individuals with HIV was significantly lower than risk of death for coinfected patients compared with the period of time from 0 to 18 months after SVR. Serero and colleagues found that noninvasive testing, such as Baveno VI and expanded Baveno VI criteria, was predictive of large esophageal varices needing treatment in patients with hepatitis B virus (HBV)-, HCV-, or HIV-related chronic liver disease compared with the gold standard of esophagogastroduodenoscopy (Abstract 533). These noninvasive tests can be used to decrease the rate of invasive procedures, especially in resource-limited settings. Mocroft and colleagues looked at rates of mortality and end-stage liver disease in patients with triple-infection with HBV (HBV surface antigen [HBsAg]+), HCV (RNA+), and HIV, compared with groups with 2 coinfections, and with HIV monoinfection (Abstract 534). Triple-infected patients had higher mortality rates than those with HIV/HBV coinfection (IRR, 0.66; 95% CI, 0.46-0.94), HIV/HCV coinfection (IRR, 0.75; 95% CI, 0.56-1.00), and HIV monoinfection (IRR, 0.49; 95% CI, 0.36-0.66), but similar mortality rates to patients with HIV/HBV infection with positive HCV antibody and negative HCV RNA (IRR, 1.05; 95% CI, 0.7-1.58). Triple-infected patients tended to have higher rates of end-stage liver disease, but this was not significantly elevated above the HIV and HCV coinfected group (HR, 0.71; 95% CI, 0.47-1.06).

Outcome Delivery of HCV and the Care Cascade

Ortega and colleagues developed models to examine the effect of COVID-19 on HCV elimination in the United States (Abstract 72). They used a general population model stratified by age and risk factor (ie, PWID) and validated it using 2019 estimates of new HCV infections. They modeled the HCV infection incidence and mortality from 2015 through 2030 with 3 scenarios: 1 model with no change to elimination strategies, 1 model with a 1-year reduction in strategies, and 1 model with a 2-year reduction in strategies. The target of 80% reduction in incidence of HCV infection was not reached in any model, even the model without any treatment interruptions. The relative reduction in HCV infection incidence was 5.5% in the 2-year disruption model (95% CI, 5.1-5.8) and 29.7% in the uninterrupted model. They modeled that there would be 990 new additional HCV infections with 1 year of disruption (95% CI, 417-1330) and 1933 new additional infections in the 2-year disruption model (95% CI, 800-2599). The target of 65% reduction in HCV infection mortality was also not reached in any model, with a relative reduction of 30.6% in the 1-year disruption model (95% CI, 21.7-38.4) and a 20.6% reduction in mortality in the 2-year disruption model (95% CI, 14.4-29.5). The authors concluded that scale-up of current HCV infection reduction efforts is needed to meet these targets.

The study authors concluded that scale-up of current HCV reduction efforts are needed to meet these elimination targets

Van Santen and colleagues used pooled cohort data of more than 45,000 people with HIV from 5 countries from 2010 to 2019 to examine whether they were on track to meet the WHO target of reducing HCV infection incidence by 30% in 2020 and 80% in 2030, as well as if there is a "treatment as prevention" effect on incidence of HCV infection (Abstract 73). They observed a 49% reduction in incidence from 2015 (time of introduction of DAAs; 0.91/100 person-years; 95% CI, 0.8-1.03) to 2019 (0.46/100 person-years; 95% CI, 0.35-0.60). Mean incidence before the introduction of DAAs was 1.27 per 100 person-years. They observed a decrease in HCV incidence of about 0.009 per 100 person-years every 6 months after the introduction of DAAS (95% CI, –0.02-–0.005). The authors concluded that most cohorts were on track to meet WHO targets and that treatment as prevention did reduce incidence of HCV infection when there was broad access to DAAs.

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Mother-to-Child Transmission of HCV

Chappell and colleagues compared the incidence of HCV infection with risk-based screening versus universal HCV screening (which is now recommended in major guidelines) among pregnant individuals (Abstract 27). They examined more than 24,000 individuals; the majority were White (about 72%-74%) and nearly half were on public insurance with Medicaid or Medicare. Overall, HCV antibody IgG testing rates increased dramatically in the universal population (81%) compared with the risk-based screening group (23%). The prevalence of IgG positivity was 1.9% in the universal population group and 1.2% in the risk-based screening group ($P<.01$). The rate of HCV RNA testing also increased in the universal group, with 95% of HCV IgG-positive groups with RNA tested, compared with the risk-based group, with 22% of IgG positive-groups with RNA tested ($P<.01$). This led to higher rates of HCV RNA positivity (indicating active HCV infection) in the universal screening group at a rate of 0.68% than in the risk-based screening group at a rate of 0.091% ($P<.01$). They found 5 infants with HCV infection in the universal screening group and 1 infant in the risk-based screening group. The authors concluded that universal screening resulted in increased detection of active HCV infection, supporting the ongoing use of this strategy.

Advances in Treatment of Hepatitis B

Epidemiology of Hepatitis B Virus

Phinius and colleagues examined rates of HBV infection in people with HIV in Botswana and found a 7.9% positivity rate with screening when using HBsAg (Abstract 543). They found that 7.2% of patients with positive HBsAg were also HBV core immunoglobulin M (HBcIgM) positive, indicating recent infection, and 13.9% of patients with HBV had HBV e antigen (HBeAg) positivity. Male sex was more associated with HBV infection (OR, 1.85; 95% CI, 1.37-2.50). They found statistically significant variation in rates of positivity among regions of Botswana.

HBV Infection Treatment

Das and colleagues presented the antiviral effect on a tenofovir long-acting prodrug formulation named NM1TFV in 2 mouse models with HBV infection (Abstract 545). After a single IM injection of NM1TFV, HBV DNA remained undetectable in the blood of infected mice up to 12 weeks, which may provide new possibilities for long-acting HBV treatment.

HBV Vaccination

Huang and colleagues examined the effect of double-dose HBV revaccination (40 µg) versus standard vaccination (20 µg) in MSM who were vaccinated against HBV as infants in Taiwan (Abstract 544). In a randomized controlled trial, they looked at men born after July 1986, when neonatal HBV vaccination was rolled out in Taiwan, with negative HBsAg, negative HBV core antibody (HBcAb), and HBV surface antigen (HBsAb) titer under 10 mIU/mL. Seventy-five percent of the patients enrolled were people with HIV, and those not on ART were excluded. Seventy percent of participants had CD4+ counts of more than 500 cells/µL, and 95% had HIV viral loads of less than 50 copies/mL. At 28 weeks, the investigators found higher seropositivity in the double-dose group (96%) than in the standard group (88%) ($P=.018$). The high-titer response rate (defined as a titer of HBsAb ≥100 mIU/mL) was higher in the double-dose group than in the standard group at week 24 (86% vs 74%, respectively; $P=–.013$) and at week 48 (77% vs 61%, respectively; $P=.003$). They also observed similar response rates to HBV vaccination in persons with HIV and CD4+ counts of more than 500 cells/µL and in MSM who were HIV negative.

Jain and colleagues presented data on HBV vaccination in people with HIV (Abstract 546). In addition to studying rates of HBV vaccination, they also used Cox proportional hazards models to determine associations with HBsAb positivity after vaccination and various factors. CD4+ counts of more than 200 cells/µL were associated with a higher rate of HBsAb positivity (aOR, 1.81; 95% CI, 1.17-2.79; $P=.008$). Hispanic White men had lower rates of HBsAb positivity (aOR, 0.55; 95% CI, 0.30-1.00; $P=.050$). Jain

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and colleagues also looked at cohort data to examine predictors of HBV infection in people with HIV (Abstract 548). HCV infection was correlated with higher rates of HBV infection (aOR, 3.08; 95% CI, 1.72-5.51; *P*=.0002), as well as nonhepatocellular carcinoma malignancies (aOR, 1.96; 95% CI, 1.13-3.42; *P*=.02). The largest risk factor for HBV acquisition was nonimmune HBsAb titer. Interestingly, the investigators did not observe a protective effect of HBV-active ART on HBV acquisition, but it is not clear whether patients were adherent at the time of acquisition. Prior studies have shown that ART can function as effective HBV prophylaxis.[10-13] An interesting area of future study would be trying to understand why HBV-active medications were not associated with decreased rates of HBV infection in people with HIV in this cohort.

Mother-to-Child Transmission of HBV

Segeral and colleagues conducted a single-arm prospective trial in Cambodia to prevent mother-to-child transmission of HBV in women who were HBsAg-positive without relying on the use of HBV immunoglobulin (HBIg) for the infant due to difficulty in access to this intervention (Abstract 28). Their 3-pronged approach included use of rapid diagnostic tests for HBsAg, HBeAg, and alanine aminotransferase (ALT) level with use of tenofovir from 24 weeks onwards if HBeAg positive or HBeAg negative with ALT of 40 IU/L or greater, as well as HBV vaccination for all infants within 2 hours of birth. The primary outcome was proportion of infants with positive HBsAg and HBV DNA viral load at 6 months. They enrolled nearly 1200 pregnant woman who were HBsAg-positive in the study, with a median age of 29 years and at a median of 23 weeks of gestation. Of these women, 338 were eligible for TDF. The median HBV DNA level was 7.9 $\log_{10}$ IU/mL in the TDF-eligible group and 2.5 $\log_{10}$ IU/mL in the TDF-ineligible group. The overall rate of infants with HBV was 1.26%; in the 85% of infants who did not receive HBIg, the rate was 1.48% (95% CI, 0.40-3.74). The rate of HBV-positive infants was 0% in women who received TDF for more than 4 weeks before delivery (95% CI, 0-1.41) and 8.33% for those women who were TDF-eligible but received treatment for fewer than 4 weeks before delivery (95% CI, 1.75-22.5). The rate of HBV in infants born to women ineligible for TDF was similar in those who did not receive HBIg (1.06%; 95% CI, 0.39-2.30) and all infants born to women ineligible for TDF (0.98%; 95% CI, 0.4-2.02). The study authors concluded that TDF given to women who are eligible for TDF for more than 4 weeks prior to delivery was effective at preventing transmission of HBV to the infant in the absence of HBIg use.

The study authors concluded that TDF given to women who are eligible for TDF for more than 4 weeks prior to delivery was effective at preventing transmission of HBV to the infant in the absence of HBIg use

Selected Issues in Maternal and Pediatric Health

HIV, COVID-19, and Maternal/Pediatric Health Outcomes

Data on the impact of the HIV and COVID-19 pandemics on birth outcomes among women with HIV, particularly in settings with high HIV prevalence, are limited. Maternal deaths and infant adverse birth outcomes among women in Botswana who were routinely screened for COVID-19 at delivery were compared by maternal COVID-19 status, COVID-19 variant (pre-Delta vs Delta), and HIV serostatus during the 2020 to 2021 period when access to COVID-19 vaccinations in the country was limited (Abstract 29). Data were analyzed from the Tsepamo study, which conducted birth outcomes surveillance among women at 13 government hospital sites throughout Botswana. The analysis included

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women who had singleton deliveries, known HIV serostatus, and received COVID-19 screening using rapid antigen or PCR testing 14 days before and up to 3 days after delivery. Of 20,410 deliveries during the study period, 11,483 (56%) were screened for COVID-19. Overall, 4.7% of the women who had been screened for COVID-19 tested positive, with

Infants born to women with HIV who had COVID-19 had the highest risk for most adverse birth outcomes

women with HIV more likely to test positive at delivery than women without HIV (5.6% vs 4.2%, respectively; $P<.01$). Among women with HIV, ART use was highly prevalent, with 97% of the women receiving ART and more than 75% initiating ART prior to conception. Maternal mortality was higher in women with COVID-19, with maternal deaths occurring in 19 women with COVID-19 (4%) versus 12 women without COVID-19 (0.1%) (age-adjusted risk ratio [aRR], 31.6; 95% CI, 15.4-64.7); the rates did not differ by HIV serostatus. Maternal mortality was higher during the wave of the Delta COVID-19 variant than during pre-Delta waves. Rates of any adverse birth outcomes (defined as preterm delivery, small for gestational age, stillbirth, or neonatal death) were significantly higher among infants born to women with COVID-19 than among women without COVID-19 (34.5% vs 26.6%, respectively; aRR, 1.31; 95% CI, 1.16-1.48). Specifically, rates of preterm delivery (21.4% vs 13.4%; aRR, 1.60; 95% CI, 1.35-1.90) and stillbirth (5.6% vs 2.7%; aRR, 1.97; 95% CI, 1.37-2.84) were higher among infants born to women with COVID-19. Rates of any adverse birth outcomes were highest among infants born to women with HIV who also had COVID-19 (43.1% vs 30.4%; aRR, 1.78; 95% CI, 1.47-2.16). The authors concluded that maternal mortality was higher in women with COVID-19, infants born to women with COVID-19 had more adverse birth outcomes, and infants born to women with HIV who had COVID-19 had the highest risk for most adverse birth outcomes. The authors also emphasized further research is needed to understand the biologic interactions between COVID-19, HIV, and adverse birth outcomes, as well as to evaluate how care delivery barriers during the COVID-19 pandemic in Botswana impacted these findings.

Other research findings on the impact of COVID-19 on maternal and child health were presented. In Abstract 671, the authors compared adverse pregnancy outcomes in pregnant women with and without SARS-CoV-2 infection in Kenya. Of 998 women who completed pregnancy follow-up, 169 (22%) tested positive by PCR for SARS-CoV-2, of whom 93 (55%) were symptomatic. Fourteen pregnant women with COVID-19 required hospitalization, though none necessitated intensive care unit (ICU) admission. Very low birth weight (<1500 g), very preterm birth (<34 weeks), and preterm birth (<37 weeks) were significantly more common among women with COVID-19 than among those without COVID-19. The study did not find a significant association between COVID-19 in pregnancy and stillbirths, prenatal deaths, hypertensive disorders of pregnancy, preeclampsia, or eclampsia.

In Abstract 672, the clinical outcomes of SARS-CoV-2 infection and pregnancy were evaluated in a retrospective cohort study of 1315 pregnant and nonpregnant women 18 years old or older who were hospitalized at health facilities in 6 sub-Saharan African countries and who were tested for SARS-CoV-2 infection with PCR. Among the women who had SARS-CoV-2 infection, pregnancy was associated with an increased risk of ICU admission and oxygen supplementation. Among pregnant women, those who had SARS-CoV-2 infection had increased risk of ICU admission, oxygen supplementation, and in-hospital maternal mortality compared with those who were not infected with SARS-CoV-2. Pregnant women who had SARS-CoV-2 infection were more likely to deliver by cesarean section than pregnant women who did not have SARS-CoV-2 infection. In this study, preterm birth, low birth weight, and neonatal mortality did not differ significantly by SARS-CoV-2 infection status.

COVID-19 Treatment in Children

Several abstracts covered therapeutics for COVID-19 in the pediatric population. Abstract 743 presented results from an open-label, phase III, clinical trial addendum (BLAZE-1 [A Study of LY3819253 {LY-CoV555} and LY3832479 {LY-CoV016} in Participants With Mild to Moderate COVID-19 Illness]) that evaluated the safety, pharmacokinetics (PK), and efficacy of SARS-CoV-2 neutralizing monoclonal antibodies bamlanivimab (BAM) and etesevimab (ETE) administered together (BAM+ETE) in 111 children younger than 18 years of age who were at increased risk for severe COVID-19. BAM plus ETE received emergency use authorization by the FDA in December 2021 for treatment of mild-to-moderate COVID-19 in patients younger than 12 years of age. Of note, BAM plus ETE is not recommended for use in areas of the United States where Omicron is the predominant variant due to its lack of efficacy against the variant. In this trial, dosing of BAM plus ETE varied by weight, with those weighing 40 kg or more receiving 700 mg BAM plus 1400 mg ETE (similar to the authorized adult dose) and those weighing less than 40 kg receiving weight-based dosing; all participants received a single-dose infusion. In children receiving weight-based dosing, PK analysis showed that drug exposures as represented by serum area under the curve for BAM and ETE were similar to those seen in adults and children aged 12 to under 18 years weighing at least 40 kg. Treatment with BAM plus ETE in children was found to be safe and well tolerated, with no reports of serious adverse events, hospitalizations, or deaths. Adverse events included 1 report of an infusion site extravasation related to study drug that was moderate in severity, 1 report of a rash that occurred more than 24 hours after infusion, and 1 report of blood creatine phosphokinase elevation on day 1 that was graded as severe and that decreased to within normal range by day 29. There were no new safety concerns of BAM plus ETE in children aged 0 to under 12 years. BAM plus ETE treatment resulted in a decrease in HIV viral load,, and the median time to symptom resolution was 5 days.

In Abstract 744, safety, clinical, and virologic outcome data were presented from the ongoing CARAVAN (Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Efficacy of Remdesivir [GS-5734] in Participants From Birth to ≤18 Years of Age With Coronavirus Disease 2019 [COVID-19]) open-label, single-arm study of remdesivir in 53 hospitalized infants and children under 18 years of age with COVID-19. Remdesivir was administered intravenously for up to 10 days, with dosing stratified by weight. The median age of the children was 7 years; at baseline, 76% of the children were on supplemental oxygen, including 23% who received invasive ventilation and 34% who had high-flow oxygen. The median number of doses of remdesivir received by the children was 5. Serious adverse events were reported in 21% of the children, with none that were related to the study drug. Two children who had transaminitis at baseline had elevation in ALT level, which led to study drug discontinuation; there were 2 deaths that occurred during the 30-day study period. Grade 3 or higher laboratory abnormalities, most commonly decreased hemoglobin and decreased estimated glomerular filtration rate, were reported in 42% of the children. No new safety concerns were reported. Overall, 25% (3 of 12) of the children who received invasive ventilation at baseline continued to be on invasive ventilation at the last available study evaluation. A majority (85%) had clinical improvement (≥2-point increase from baseline) at their last evaluation. The recovery rate (score of 6 or 7) was 83% at their last evaluation. The median time to hospital discharge was 8 days. The time to first confirmed negative SARS-CoV-2 PCR result from nasal or oropharyngeal specimens was 5 and 7 days in the 2 cohorts of children with available data.

HIV, ART, and Pregnancy Outcomes

Stunted growth in infancy has negative implications on cognitive development and adult height. A post hoc analysis of IMPAACT 2010, a randomized open-label clinical trial of 643 pregnant women with HIV in 9 countries, assessed the impact of 3 different maternal ART regimens during pregnancy and breastfeeding on infant growth through 50 weeks postpartum (Abstract 30). Women were randomly assigned to initiate 1 of the following maternal

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ART regimens at 14 to 28 weeks gestation: (1) DTG plus TAF/FTC, (2) DTG plus TDF/FTC, or (3) EFV/TDF/FTC. Infant length and weight were measured, and Z-scores for length-for-age (LAZ), weight-for-age (WAZ), and weight-for-length (WHZ) were calculated according to WHO standards. Overall, 78% of the infants were initiated on breastfeeding and continued for a median of 50 weeks; only 4 infants (0.6%) acquired HIV infection. Infants in the EFV/TDF/FTC arm were smaller than in the 2 DTG-containing arms, with LAZ and WAZ scores lower than the DTG arms. Growth was similar in infants exposed to maternal TDF versus TAF with DTG/FTC, with no mean differences between the 2 arms in LAZ or WAZ scores at weeks 26 and 50. There were no differences in mean WHZ scores across the 3 arms. Rates of severe stunting, defined as LAZ score below –2, were high across the 3 ART arms, with a higher proportion of infants in the EFV/TDF/FTC arm experiencing severe stunting than in the DTG plus TAF/FTC and DTG plus TDF/FTC arms at weeks 26 and 50 (20% vs 15% and 15% at week 26, and 21% vs 13% and 14% at week 50, respectively). The authors postulated that a potential mechanism to explain this finding is the differential weight gain by ART regimen experienced by the women during pregnancy.

Early Treatment and HIV Reservoirs in Children

A major obstacle to ART-free remission and cure for HIV is the latent reservoir for HIV in resting memory CD4+ T cells and macrophages.[14] Research efforts have been ongoing to develop strategies to restrict and eradicate the latent HIV reservoir, including pediatric-specific approaches to achieve long-term ART-free remission in children with early intensive treatment. Data on 2-year virologic outcomes of very early ART and potential for reduction of the latent HIV reservoir in infants in the IMPAACT P1115 (Very Early Intensive Treatment of HIV-Infected Infants to Achieve HIV Remission: A Phase I/II Proof-of-Concept Study) investigation were presented in Abstract 31. The ongoing prospective proof-of-concept study enrolled a total of 460 infants in 2 cohorts in 11 countries. In cohort 1,440 infants who were at high risk for HIV infection were started on pre-emptive NVP-based ART within 48 hours of birth. Of these, 34 infants who were diagnosed with in utero HIV infection were continued on ART in the study. In cohort 2, an additional 20 infants who had acquired in utero HIV infection and who had initiated NVP-based ART by age 48 hours were enrolled by age 10 days. The median age at first ART was 7.3 hours for cohort 1 (n=34) and 32.8 hours for cohort 2 (n=20). ART consisted of dual nRTIs combined with NVP, with lopinavir/ritonavir added as age appropriate; NVP was subsequently discontinued in children after 12 weeks of confirmed virologic suppression. At week 24, 75% (24 of 32) of infants in cohort 1 and 88% (15 of 17) in cohort 2 had virologic suppression (viral load <200 copies/mL). The estimated Kaplan-Meier probability of confirmed virologic suppression at age 2 years was 33% in cohort 1 and 57% in cohort 2. In infants with sustained virologic suppression at 2 years of age, 83% in cohort 1 and 100% in cohort 2 tested negative for HIV antibody; 64% in cohort 1 and 71% in cohort 2 had undetectable CA-DNA, with low HIV reservoir size that potentially allows for ART-cessation and ART-free remission. The overall estimated Kaplan-Meier probability of potential eligibility for ART interruption through age 2 years was 33% (29% in cohort 1 and 30% in cohort 2).

Pharmacokinetics, Safety, and Acceptability of New HIV Agents for Children and Youth

Treatment with bNAbs as an alternative to ART in children with HIV in Botswana was evaluated in the Tatelo (Dual bNAb Treatment in Children) proof-of-concept study (Abstract 32). The children had to be at least 96 weeks of age, receive ART continuously from less than 7 days of life (with the exception of 1 child with intrapartum HIV infection who began ART at 31 days), and have undetectable HIV RNA at less than 40 copies/mL for at least 24 weeks prior to study enrollment. The study involved 3 different steps. In step 1, which lasted 8 to 32 weeks, the children received overlapping treatment with ART (lopinavir/ritonavir-based ART) and dual bNAb IV infusions with VRC01LS and 10-1074, which were administered every 4 weeks. After at least 8 weeks of overlap therapy, ART was stopped and treatment

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with dual bNAbs was continued up to 24 weeks in step 2, with HIV viral load checked every 1 to 2 weeks. In step 3, bNAb treatment was stopped, and

Dual broadly neutralizing antibody therapy with VRC01LS and 10-1074 was found to be safe and well tolerated in children with HIV

ART was restarted for children who had an HIV viral load above 400 copies/mL or who had completed 24 weeks of bNAb treatment. Of 28 children who started step 1 of the study, 25 (89%) continued to the bNAb-only treatment (step 2); of the 3 children who did not continue, 2 experienced viral rebound on the day bNAb therapy was started and 1 had viral rebound at 4 weeks into step 1 (ART/bNAb overlap phase). Eleven children (44%) maintained an HIV RNA level below 40 copies/mL through 24 weeks of bNAb-only treatment (step 2) and after ART reinitiation (step 3). Fourteen children (56%) had viral rebound to above 400 copies/mL before completing 24 weeks of bNAb-only treatment (step 2), with a median time to failure of 4 weeks; these children were immediately restarted on ART and all achieved suppression to below 40 copies/mL at a median of 4.1 weeks from ART reinitiation. In a further comparison of the characteristics of the 11 children who maintained viral suppression through 24 weeks of bNAb-only treatment with the 13 who did not, the authors found that children who had a longer ART and bNAb overlap period, who enrolled earlier in the study with longer continuous viral suppression on ART, and who had lower mean HIV DNA in peripheral blood mononuclear cells (as a marker for viral reservoir) were more likely to achieve treatment success. Dual bNAb therapy was found to be safe and well tolerated, with no infusion-related reactions and five grade 3 events reported, including 1 neutropenia that was possibly related to study drug.

In Abstract 732, 24-week safety and PK profile of VRC07-523LS, a long-acting bNAb targeting the CD4 binding site of the HIV envelope protein, in infants exposed to HIV was presented. Formula-fed infants in cohort 1 received VRC07-523LS 80 mg subcutaneously (SC) as a single dose within 72 hours of birth, and breastfed infants in cohort 2 were administered 80 mg SC within 5 days of birth and 100 mg SC at week 12 if still breastfeeding. VRC07-523LS SC was found to be safe and well tolerated in infants, with local site reactions that were grade 1 and 2 in severity and most resolving within 24 hours; no grade 3 or higher adverse events were related to the study drug. PK data showed that VRC07-523LS had rapid absorption and slow elimination, with a T1/2 of approximately 34 hours, which allows for dosing every 3 months to achieve target levels above 10 µg/mL.

Abstract 737 provided PK and week 4 safety results from the IMPAACT 2019 phase I/II open-label dose confirmation study for once-daily ABC/DTG/3TC in dispersible tablet form in 14 children weighing 6 kg to less than 14 kg. No grade 3 or higher adverse events related to study drug were reported, and no study drug discontinuations occurred as a result of adverse effects. The PK profile of the dispersible tablet formulation was favorable and met study criteria.

Safety, tolerability, and PK data from the IMPAACT 2017 (MOCHA [More Options for Children and Adolescents]) phase I/II open-label trial of CAB-LA and RPV in adolescents with HIV were presented in Abstract 738. Adolescents aged between 12 to 18 years who were virologically suppressed on stable ART were enrolled into cohort 1C (CAB) (n=8) or cohort 1R (RPV) (n=15) based on background ART. The participants underwent a 4-week lead-in period with oral CAB (30 mg once daily) or RPV (25 mg once daily), followed by CAB-LA (600 mg/3 mL at week 4; 400 mg/2 mL at weeks 8 and 12) or RPV-LA (900 mg/3 mL at week 4; 600 mg/2 mL at weeks 8 and 12) via IM injection in the gluteus muscle. Background ART was continued. PK samples were collected to assess oral and LA dosing. All participants in cohorts 1C and 1R were virologically suppressed (HIV viral load <50 copies/mL) at week 16. Injection site reactions were reported as grade 1 or 2 in severity, with none resulting in study product

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discontinuation. There was 1 grade 3 adverse event in each cohort that was considered related to the study drug (insomnia in cohort 1C and hypersensitivity in cohort 1R, which resulted in withdrawal from the study). The PK parameters met prespecified study targets. The authors concluded that CAB-LA or RPV-LA IM administration in combination with background ART in adolescents achieved drug levels that were comparable to those observed in adults receiving monthly IM dose regimens, with no new or unanticipated safety issues found. In Abstract 739, acceptability of and experiences related to CAB-LA and RPV-LA IM injections were evaluated using in-depth interviews with 21 adolescents enrolled in the IMPAACT 2017 MOCHA Study and their parents or caregivers. The participants recounted the relative advantages of LA injections to oral pills, such as not having to remember to take pills, avoiding the stress of monitoring daily adherence to pills, and not having to be concerned about hiding pills from peers. Concerns for using LA agents for long-term ART included apprehensions about maintaining a routine injection schedule with competing interests such as school, extracurricular activities, and work.

HIV Viral Load Testing in Children

In Abstract 33, Patel and colleagues presented results from a randomized controlled clinical trial evaluating the impact of an intervention involving POC HIV viral load testing every 3 months, targeted DRM testing for HIV viral load of 1000 copies/mL or greater, and clinical management support for practitioners versus standard of care following Kenyan national guidelines (HIV RNA testing every 6 months; DRM testing was restricted to second-line ART failure using a centralized approval system) over 12 months in children aged 1 to 14 years receiving first- or second-line ART in Kenya. Of the 704 children who were enrolled, the mean age was 9 years, 76% of the children had baseline viral suppression, and the median duration on ART was 5.8 years. Viral suppression at 12 months (defined as HIV RNA level <1000 copies/mL) was similarly high in both groups, with 90.4% (283 of 313) in the intervention arm and 91.7% (287 of 313) in the standard of care arm (RR, 0.99; 95% CI, 0.94-1.03). Among children in the intervention arm, 138 episodes of viremia from 81 children were detected; 107 (89%) samples had DRM testing, with 100% of samples having any DRM detected and 85% having any major DRM identified. Among children in the standard of care arm, 72 episodes of viremia from 56 children were found; however, only 2 samples had DRM testing, with both samples (100%) having any DRM detected and having any major DRM isolated. After any episode of nonviral suppression, there was no statistically significant difference in viral resuppression at 12 months between the 2 groups, with 69.5% (91 of 131) of children in the intervention arm versus 63.1% (101 of 160) in the standard of care arm achieving viral resuppression. The median turnaround time for viral load results was shorter in the intervention arm, with median turnaround time of 1 day in the intervention arm versus 15 days in the standard of care arm. The authors concluded that combination interventions that integrate POC viral load, DRM testing (including further research into POC DRM testing), and behavioral support for children and their families would be beneficial in optimizing ART and viral suppression in this population.

The authors dedicate this article in memory of Dr Scott M. Hammer.

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